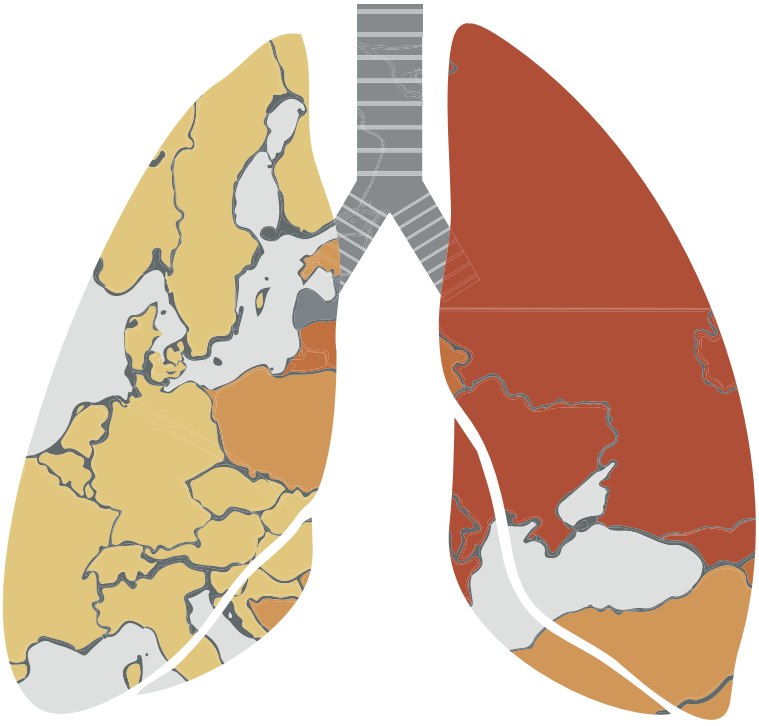
Tuberculosis in the WHO European Region, Research for Evidence-based Policies



Masoud Dara MD

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Tuberculosis in the WHO European Region, Research for Evidence-based Policies

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Tuberculosis in the WHO European Region, Research for Evidence-based Policies

Doctoral Thesis

to obtain the degree of doctor
from Radboud University Nijmegen
on the authority of the Rector Magnificus prof. dr. J.H.J.M. van Krieken,
according to the decision of the Council of Deans
to be defended in public on Monday, May 17, 2021
at 14.30 hours

by
Masoud Dara
born on September 16, 1968
in Tehran, Iran

Supervisor:
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This thesis is dedicated to

To my parents Jamshid and Zahra for their love, integrity and resilience
To my brother Majid for his support
To my daughter Eileen and my son Sam for bringing us joy, happiness and pride

Table of Contents

List of acronyms and abbreviations

AIDS: Acquired Immunodeficiency Syndrome
ART: Antiretroviral Therapy
BCG: Bacillus Calmette-Guérin
CI: Confidence Interval
DALY: Disability-Adjusted Life-Year
DST: Drug Susceptibility Testing
ECDC: European Centre for Disease Prevention and Control
ERS: European Respiratory Society
EU/EEA: European Union – European Economic Area (countries)
GFATM: Global Fund to fight AIDS, Tuberculosis and Malaria
HIV: Human Immunodeficiency Virus
IC: Infection Control
IGRA: Interferon Gamma Release Assay
IOM: International Organization of Migration
GDP: Gross Domestic Product
IUATLD: International Union Against Tuberculosis and Lung Diseases
LMICs: Low- and Middle-Income Countries
LTBI: Latent TB Infection
MDG: Millennium Development Goals
MDR-TB: Multi drug resistant tuberculosis
MoH: Ministry of Health
NGO: Non-Governmental Organization
NTP: National TB Programme
RR: Rifampicin Resistant
SDG: Sustainable Development Goals
TB: Tuberculosis
TST: Tuberculin Skin Test
UN: United Nations
UNICEF: United Nations Children's Fund
UNHLM: United Nations High Level Meeting
USAID: United States Agency for International Development
US$: United States dollar
XDR-TB: Extensively drug resistant Tuberculosis
WHO: World Health Organization

Research data management

The data provided and analyzed in the chapters 1, 2 and 5 are extracted from the annual WHO Global Tuberculosis Reports, as well as the annual ECDC-WHO/Europe Tuberculosis Surveillance and Monitoring reports, which are available on the public domain and can be freely accessed, referenced and disseminated. All WHO surveillance reports are indexed, searchable and can be retrieved and re-used. The data used in the chapter 4 are sourced from the countrywide routine surveillance and monitoring data base in line with the approval of the "National Ethics Committee and Review Board" under the Ministry of Health of Republic of Uzbekistan. This study satisfied the criteria for reports using routinely collected programmatic data set by the Médecins Sans Frontières Ethics Review Board, Geneva, Switzerland. The raw data is restored at the Surveillance Unit of the national TB programme of Republic of Uzbekistan and can be retrieved upon request. Patient identifying information was removed prior to analysis. The data presented in the chapters 6, 7 and 8 are based on peer reviewed publications, which are listed in the references. The data in the chapter 9 are based on the results of a survey collected from the target countries in Europe, with descriptive statistics calculated where appropriate, and supplemented with qualitative information provided by responders to the survey. The study did not collect individualized information on subjects.

Abstract

Tuberculosis (TB), particularly its drug resistant forms and TB/HIV coinfection are major public health concerns in many countries of the WHO European Region. Despite progress in scale up of rapid molecular TB diagnostics and reduction of TB incidence rates, effective treatment for those suffering from drug resistant TB and/or co-infected with HIV are suboptimal, leading to unfavorable treatment outcomes and ongoing transmission. On 26 September 2018, the United Nations (UN) held its first high-level meeting on TB at its headquarters in New York and endorsed a political declaration titled *"An Urgent Global Response to a Global Epidemic"*. This thesis provides evidence for informed-decision making for improving prevention and care for TB in the WHO European region. It covers various identified priorities including: introduction and expansion of new TB treatment regimens, revamping commitment for health system approaches with people-centered care, ensuring cross border continuum of care for migrant populations, and research and innovation for new tools and equitable access. All these are key in efforts towards attaining the Sustainable Development Goal of Ending TB by 2030.

CHAPTER 1

Introduction

History of tuberculosis

Tuberculosis (TB), is caused by bacteria of the *Mycobacterium tuberculosis* complex, and is one of the oldest diseases known to affect humans and a major cause of death worldwide. Recent population genomic studies suggest that *Mycobacterium tuberculosis* may have emerged about 70,000 years ago in Africa and subsequently disseminated along with humans, expanding globally during the Neolithic Age as human density started to increase. Progenitors of *M. tuberculosis* are likely to have affected prehominids.[1] TB most often affects the lungs, although other organs are involved in up to one-third of cases. If properly treated, TB caused by drug-susceptible strains is readily curable. If untreated, the disease may be fatal in 50–65% of cases within five years.[1] Transmission of *Mycobacterium tuberculosis* mainly takes place through airborne spread of droplet nuclei produced by patients with infectious pulmonary TB and its subsequent inhalation.[2]

Global burden of tuberculosis and access to treatment

TB is one of the top ten leading causes of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS. Based on the global data published in 2019, TB caused an estimated 1.2 million deaths (range, 1.1–1.3 million) among HIV-negative people and there were an additional 251 000 deaths from TB (range, 223 000–281 000) among HIV-positive people in 2018.[3] An estimated 10 million people fell ill with TB in 2018: 90% were adults, 57% were male, 8.6% were people living with HIV and two thirds were in eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). Globally, 7 million new cases of TB were notified in 2018 – an increase from 6.4 million in 2017 and a large increase from the 5.7–5.8 million notified annually in the period 2009–2012. The latest treatment outcome data for new cases of TB show a global treatment success rate of 85% in 2017, an increase from 81% in 2016. Drug-resistant TB is a continuing threat. Globally in 2018, an estimated 3.4% (95% confidence interval [CI]: 2.5–4.4%) of new cases and 18% (95% CI: 7.6–31%) of previously treated cases had multidrug-resistant TB (MDR-TB) or Rifampicin Resistant (RR-TB). In 2018, there were 484 000 incident cases with resistance to rifampicin (RR-TB) (range, 417 000–556 000), the most effective first-line drug, of which 78% had MDR-TB, strains resistant to rifampicin and isoniazid which are the two most effective drugs used for first-line treatment. Three countries accounted for almost half of the world's cases of MDR/RR-TB: India (27%), China (14%) and the Russian Federation (9%). About 1.7 billion people, 23% of the world's population, are estimated to have a latent TB infection (LTBI) and are thus at risk of developing active TB disease during their lifetime. A total of 477 461 TB cases among HIV-positive people were reported, of which 86% were on antiretroviral therapy (ART). In 119 low- and middle-income countries that reported data (and accounted for 97% of reported TB cases globally), funding reached US$ 6.8 billion in 2019, up from US$ 6.4 billion in 2018 and US$ 3.5 billion in 2006. However, the amount in 2019 was US$ 3.3 billion less than the US$ 10.1 billion estimated to be required in the

Stop TB Partnership's Global Plan to End TB 2018–2022[4], and only just over half of the global target of at least US$ 13 billion per year by 2022 that was agreed at the UN High Level Meeting (UNHLM) on TB[1]. The latest treatment outcome data show success rates of 85% for TB, 75% for HIV-associated TB, 56% for MDR/RR-TB and 39% for extensively drug-resistant TB.[3]

Tuberculosis in the WHO European region

In 2018, 259 000 incident TB cases (225 000–296 000) estimated in the WHO European Region, corresponding to 28 cases (24–32) per 100 000 population. During the period 2009–2018 and between 2014 and 2018, the average annual decline in the TB incidence rate was 5.1%, which is the fastest decline among all WHO Regions. If this pace of decline is maintained, the Region will achieve the 2020 End TB Strategy milestone to reduce TB incidence rate in 2020 by 20% against the 2015 baseline, even though it will fall slightly short of reaching the Regional action plan target of a 25% reduction in the TB incidence rate.[5] The WHO European region has less than 3% of the global burden of TB. There is also a wide variation in notification across the region from zero in Monaco and Saint Marino to 116 per 100 000 population in Kyrgyzstan (Figure 1). TB is seen mainly among young males in eastern Europe and central Asia. In western Europe, TB is mainly found among foreign-born individuals and older adults of the native population. In some low incidence countries, up to 90% of TB incident cases are found among foreign born individuals.[5]

Like other regions, incarceration significantly increases the risk of TB (22 times higher rate of TB incidence in prisons than in the general population). The average TB notification rate in prisons in the region was 749 per 100 000 population.[5]

About 85% of incident TB cases in Europe occurs in the 18 high-priority countries[2]. Tuberculosis notification in the WHO European region increased sharply from 1990 onwards, reaching a peak in 1999. Since 2000, TB notification in the region has been decreasing. (Figure 2)

[1] https://www.who.int/tb/unhlmonTBDeclaration.pdf

[2] The 18 high-priority countries (HPC) are: Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Republic of Moldova, Romania, Russian Federation, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan.

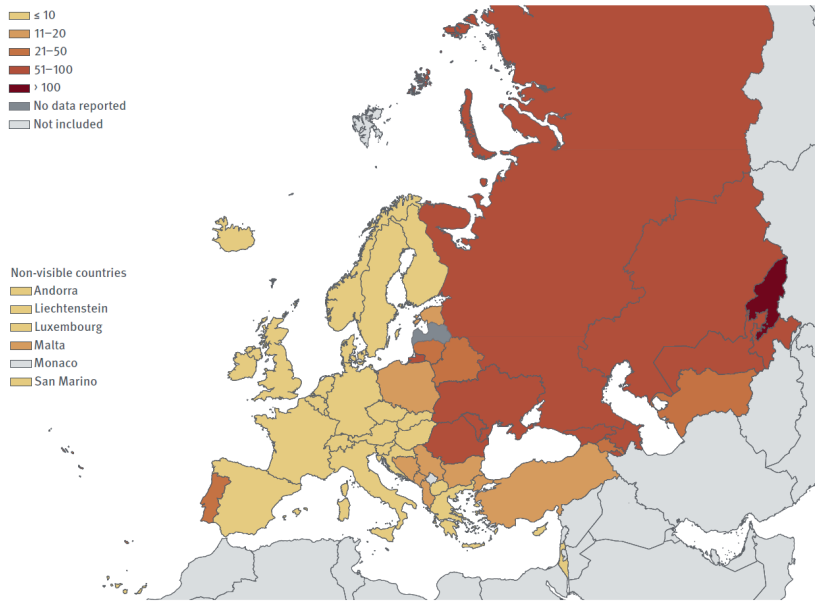


Figure 1. TB notification per 100 000 population, WHO European Region 2018

Source: European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2020 - 2018 data

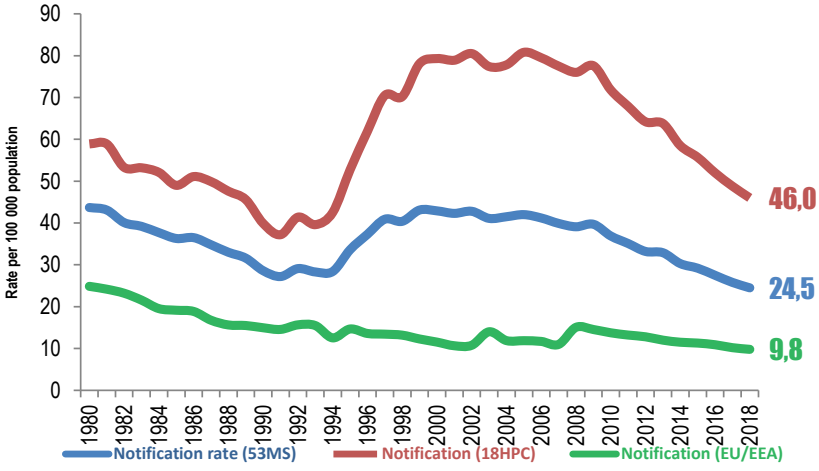


Figure 2. TB notification per 100 000 population, WHO European Region (1980-2018)

Treatment success rates among combined cohorts of new cases and relapses notified in the WHO European Region in 2018 was 78%. There were an estimated 23 000 TB deaths among HIV-negative people in the European Region in 2018, equivalent to 2.5 deaths per 100 000 population (range 2.4–2.6). Considerable variation was seen across the

Region, ranging from less than one TB death per 100 000 population in western European countries to more than 10 per 100 000 in High Priority Countries (HPC) of the Region. Between 2009 and 2018, the TB mortality rate at regional level fell cumulatively by 57%, from 5.8 to 2.5 deaths per 100 000 population, which is a decline of 9.1% per year on average. This decline was over 12% between 2017 and 2018, which is notably higher than the global rate of decline for TB mortality (3.6% between 2017 and 2018). With a cumulative reduction of 26% between 2015 and 2018, the Region is on track to reach the End TB Strategy milestone of a 35% reduction in the total number of TB deaths between 2015 and 2020. The alarmingly high rates of rifampicin resistant and MDR-TB in most of the east European and central Asian countries represent one of the main challenges of TB control. Nine out of 30 countries with the highest MDR-TB burden in the world are in the WHO European Region[3]. For 2018, drug-susceptibility testing (DST) reporting completeness was 74.6% for the first-line TB drugs, isoniazid and rifampicin.[5] Second-line DST reporting completeness was 100% for the countries that reported at least one MDR-TB case. An estimated 18% (95% CI: 16–19%) of newly diagnosed patients and 54% (95% CI: 47–61%) of previously treated patients had RR/MDR-TB. 19.2% of pulmonary MDR-TB cases had XDR-TB in 2018. In absolute numbers, XDR-TB cases among pulmonary TB cases increased from 999 in 2014 to 6 672 in 2018, largely due to the increase in the number of countries reporting on second-line DST data.[5]

In 2018, there were an estimated 77 000 new cases of rifampicin-resistant and multidrug-resistant TB (RR/MDR-TB) in the Region, with 49 000 estimated among notified bacteriologically-confirmed pulmonary TB patients. This represents around 16% of the 484 000 global RR/MDR-TB burden in the same cohort. The proportion of RR/MDR-TB among new and previously-treated TB cases in the Region also significantly exceeds the global average, with 18% in new and 54% in previously-treated cases compared to 3.4% and 18% respectively.

Of the 49 001 laboratory-confirmed RR/MDR-TB patients notified, 43 813 (89.4%) were enrolled into MDR-TB treatment programmes.[5] In 2018, treatment success rate of MDR/RR-TB patients increased compared to previous year from 51.5% to 57.6%, (Figure 3), however it is still below the regional target of 75%.[6] The treatment success rate for RR/MDR-TB patients was higher in non-EU/EEA countries than in the EU/EEA (57.6% versus 49.9%). WHO European Region is the only Region with significant increase in the number of new HIV infections.[7] Of the 203 006 new and relapse TB patients notified in the reporting countries, 185 673 were screened for HIV (91.5%). A total of 24 365 TB cases were detected with HIV-positive status, representing 13.1% of those tested. [5]

[3] Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Republic of Moldova, Russian Federation, Tajikistan, Ukraine and Uzbekistan.

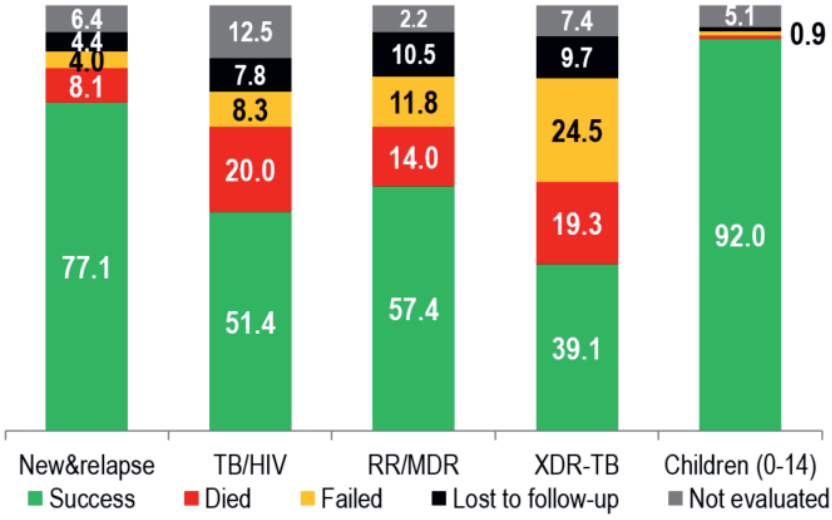


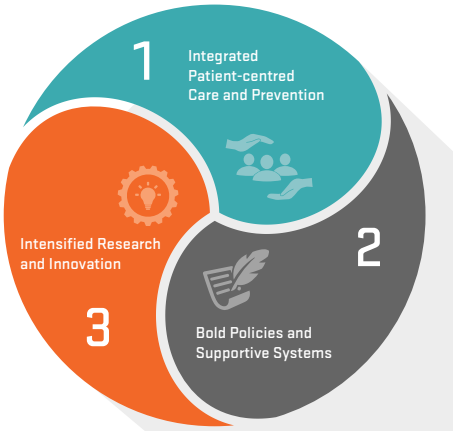
Figure 3. Treatment outcomes among new and relapse, TB/HIV co-infected, MDR/RR-TB, XDR-TB patients and children, WHO European Region, 2020 data of 2018 cohorts

Source: European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2020

Regional and Country Action Plans

To address the challenges, since 2010, the WHO Regional Office for Europe, in consultation with national and international partners has developed two consecutive Action Plans. The Consolidated Action Plan to Prevent and Combat M/XDR-TB 2011-2015 and the Tuberculosis Action Plan for the WHO European Region 2016-2020, which are both aligned with the global strategies. The plans take into account the region-specific aspects and are endorsed by all Member States at the WHO Regional Committee for Europe in September 2010 and September 2015 respectively.[6,8] Most countries of the Region have adapted these regional plans to their national context.

The Tuberculosis Action Plan for WHO European Region 2016–2020 sets a regional goal of ending the spread of drug-susceptible and drug-resistant TB by achieving universal access to quality prevention, diagnosis and treatment in all Member States of the Region. The Plan contains six strategic directions and 13 major activities grouped under three areas of intervention: integrated patient-centered care, bold policies and research and innovation (Figure 4). The Plan provides national and international partners with a framework for the coordination of roles and responsibility at regional and country level.



1. Full scale-up of rapid diagnosis
2. Rapid uptake of new medicines
3. Expanding patient- and people-centered models of care
4. Shorter and more effective treatment regimens
5. Research for new tools
6. Intersectoral approach to address inequities

Figure 4. Key Strategic directions and operational priorities of the Tuberculosis Action Plan for the WHO European Region 2016-2020

Under this Action Plan, targets to be achieved by 2020 are: a 35% reduction in TB deaths, a 25% reduction in TB incidence rate and a 75% treatment success rate among MDR-TB patients. The region is on track with achieving both reduction of mortality and incidence, however treatment success for MDR-TB is well below the target, with only 57% of MDR-TB successfully treated.

Progress and challenges

The WHO European region has the fastest decline of TB mortality and incidence rates among all WHO regions.[5] Through intensive national and international cooperation and collaboration, TB prevention and care efforts are stepped up, treatment success is gradually increasing, however not at the desired speed. Drug resistant TB is not fully addressed with only about 57% of those patients being successfully treated. Stigmatization leads to poor health seeking behavior in many settings.[9] Social determinants of the disease are not fully addressed, and TB continues to affect marginalized population and the hardest hit are the poor. Multisectoral approaches in line with Health 2020[10] and the UN Common Position to end HIV, TB and viral Hepatitis[11] are not fully implemented. Overreliance on hospitalization is among the underlying factors of nosocomial transmission. Gelmanova IY *et al* in Tomsk in the Russian Federation found out that patients who began treatment in the hospital setting or who were hospitalized later during their treatment course had a substantially higher risk of developing multidrug-resistant TB than those who were treated as outpatients.[12] Bonnet M *et al* have documented in their setting that despite big efforts, good hospitalization conditions, social support, and early management of side effects, patients had difficulties in coping with long hospitalization stays.[13] In most countries, services are designed based on the inputs (number of beds), rather than outcomes

(how many patients are fully cured). This is a disincentive for ambulatory care and lack of adequate patient-friendly services for example by providing treatment at places or times that are most convenient to patients. There is no functioning mechanism of cross border TB control and care and the migrants in the eastern part of the region often lack services they need.[14] TB in prisons is another key challenge which can turn into opportunities for better impact, if prisons provide quality and timely diagnosis and treatment.

Evidence gaps for guiding policy adaptation in the WHO European region

Drug resistant tuberculosis is the major barrier to ending TB in Europe. There are evidence gaps in determining the most cost-effective policies and practices to prevent and control drug resistant TB. The region has one of the highest rates of unfavorable outcomes globally. In addition to unnecessary loss of lives, this can lead to emergence of drug resistance, therefore it is important to review various determinants, which play role in hindering achievement of the WHO targets of treatment success. In order for TB prevention and care efforts to be effective, the national programmes and key partners are to address the needs of special populations, who are often left outside the realms of routine health services. Migrants and refugees in low to middle incidence countries and prisoners in many countries are among the key vulnerable groups for TB infection and disease, and there are gaps in effective and efficient strategies for early detection and treatment for them. In the absence of a new vaccine, the role of BCG vaccine in prevention of TB needs to be examined.

Specific evidence generated by this thesis

This thesis presents an overview of several areas where evidence has been built and contributed to policies. These include the cost effectiveness of the five-year Regional Action Plan to Prevent and Control M/XDR-TB with a methodology which can be applied to future action plans to end and ultimately eliminate TB, drug resistant TB and TB/HIV coinfection. Building on an in-depth five-year analysis in a high TB priority country (Uzbekistan), the factors associated with unfavorable outcomes in new and previously treated TB are presented. As unfavorable outcomes result in reduced patient survival and development of drug resistant TB, these findings are relevant on a wider level. With a thorough analysis of an array of unfavorable outcomes, measures to address the laboratory, clinical and programmatic shortcomings at national and subnational levels are formulated. This approach can be applied to other countries of the WHO European Region to improve performance of national programmes. Reviewing the trends, challenges and possible interventions to address the drug resistant TB as a major challenge in the Region is presented and this highlights evidence that can be integrated into policies. Improving early detection and treatment outcomes for drug resistance and drug susceptible are to be prioritized; The TB situation in prisons and the challenges and research gaps in implementation of the WHO End TB strategy in prisons are presented. Such evidence is

key to reducing missed TB cases and achieving the WHO target of ensuring that 90% of detected TB cases achieve treatment success. Following the launch of the global roadmap on childhood TB, we reviewed the TB situation in children and relevant policies in the 18 high TB priority countries. Most countries are under-diagnosing TB among children and policies and practices are often outdated. Based on the data and existing evidence, a roadmap to address TB in children in Europe is proposed and the role of BCG is reviewed. This can guide implementation strategies. With appropriate use of available laboratory tests and clinical examination, early and accurate detection of active and latent among children are to be further improved. Finally, in response to rapid increase of migration to Europe, an overview of TB screening policies and practices among refugees and asylum seekers in Europe is presented. This provides an account of country challenges with diverse policies and practices, inadequate screening, and insufficient management for TB in several countries, calling for more harmonized efforts, and closer collaboration among the countries in the Region. This is a highly topical area and has a bearing on cross-border TB transmission and control.

Outline of the thesis

Aims and objectives

The aim of the research projects that constitute this thesis is to generate and use evidence to improve the management of TB in the WHO European region, through implementation of the three pillars of the End TB strategy (Integrated patient care, Bold Policies and Research and Innovation). These studies were conducted in line with the global End TB strategy and the regional action plans. They fit well into the context of the sustainable development goals and the principle of ensuring equity (Figure 5). The specific objectives are to:

1. To review the epidemiology of tuberculosis in WHO European Region, the public health response and the cost effectiveness of MDR-TB prevention and control Plan: These are covered in the chapters two and three. We specifically review the TB epidemiological situation with the link to localization of the disease and based on data from surveillance, modeling and health financing, the cost effectiveness of interventions is assessed and their impact on lives saved and economic gains.
2. To review how TB treatment outcomes can be improved in various TB categories: This is covered in chapters four and five. In chapter four, we review national and subnational data from a high TB incidence country and discuss the unfavorable outcomes which can lead to increased suffering, unnecessary deaths, ongoing transmission and emergence of drug resistance. Unfavorable outcomes also negatively affect the credibility of the TB programme in the eyes of patients and the community. In chapter five we provide analysis of the situation in the eastern Europe and central Asia.

3. To review the role of BCG immunization in prevention of TB: In chapter six we discuss the evidence of currently available vaccine in children.
4. To analyze the policies and practices of addressing TB in vulnerable populations: In chapters seven, eight and nine, we analyze these aspects in terms of TB prevention and care in prison setting, in children and among migrant populations.

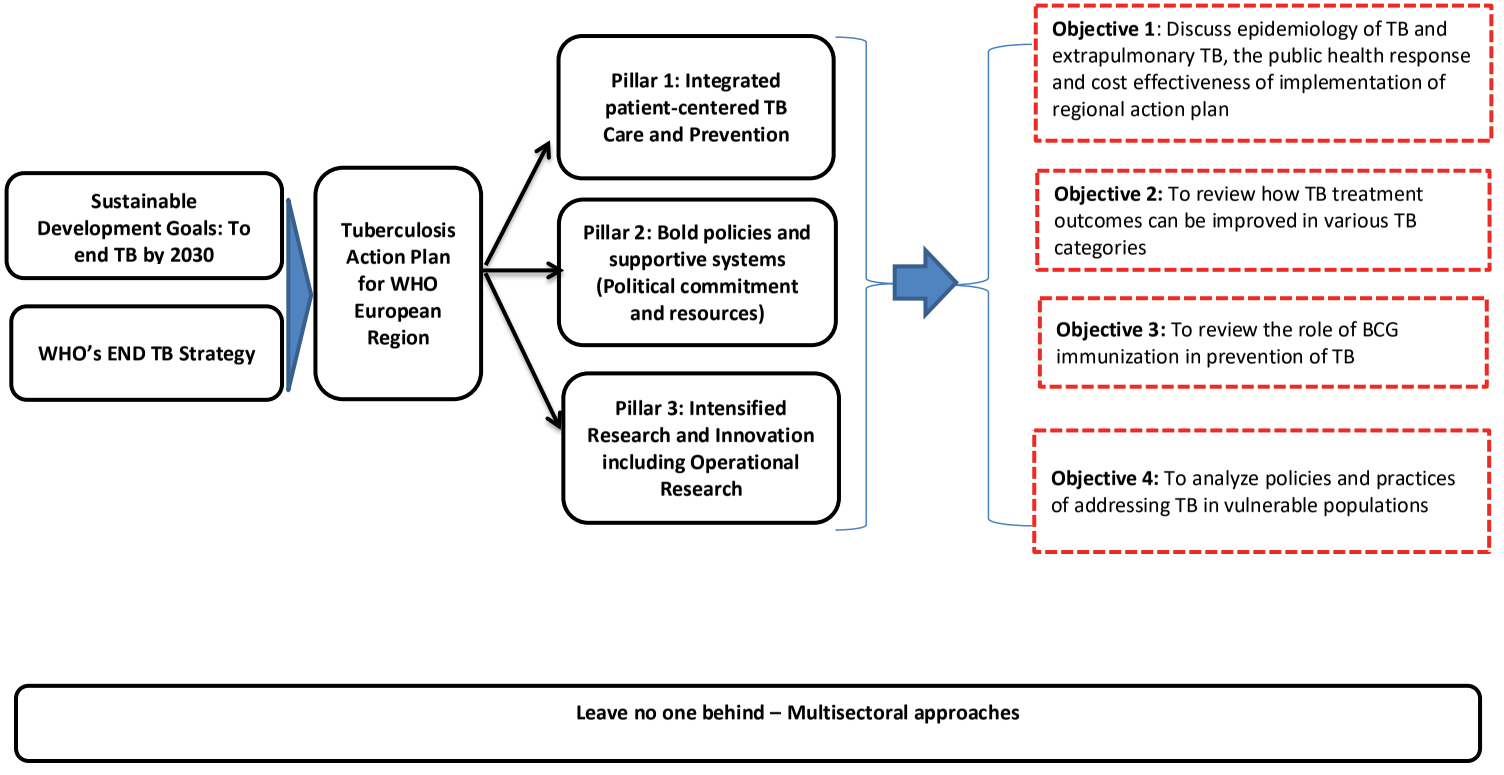


Figure 5. Conceptual framework of this thesis

Specific setting of the studies

All the studies under this thesis have been conducted in the WHO European Region. Globally, WHO Member States are grouped into six regions (Figure 6). The WHO European Region consists of 53 Member States expanding from Atlantic Ocean to Pacific Ocean and is home to more than 900 million population.[15] The countries of the WHO European region are among the most diverse regions in terms of gross national income, development index and health systems structure. The industrial revolution of the early 20s, the collapse of Soviet Union in the 90s, and migration from high TB incidence countries have played important roles in changing the tuberculosis epidemic situation in the Region.

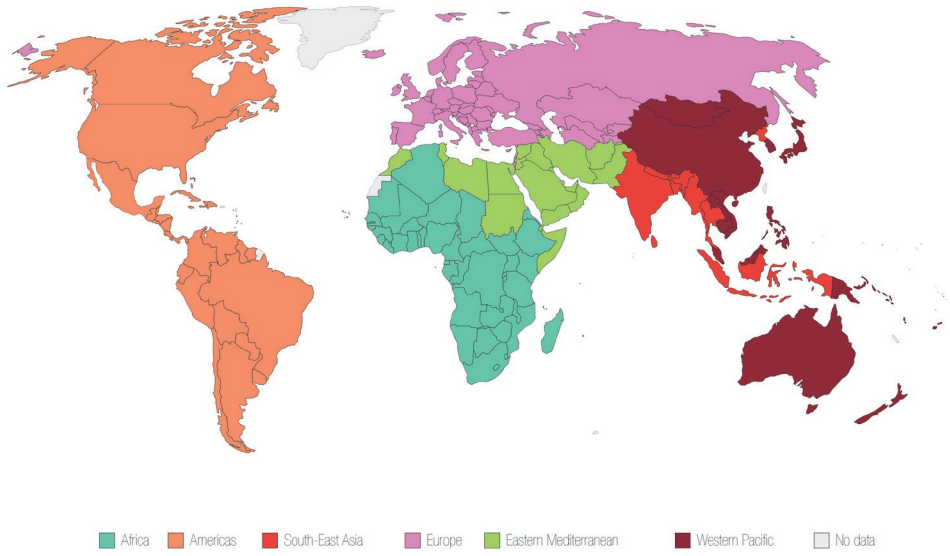


Figure 6. WHO Regions

Source: https://ourworldindata.org/grapher/who-regions and http://www.who.int/about/regions/en

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CHAPTER 2

2

Epidemiology of tuberculosis in the WHO European Region and the public health response

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Abstract

Purpose: To provide an overview of the tuberculosis (TB) and multi-drug resistant tuberculosis (MDR-TB) in the WHO European Region and evolution of public health response with focus on extra-pulmonary tuberculosis and Pott's disease.

Methods: Authors reviewed regional strategic documents related to TB. The epidemiologic data were reviewed and analyzed.

Results: Treatment success rates have been decreasing and MDR-TB rates have been increasing in the WHO European Region during the past five years. In the absence of associated pulmonary TB, Pott's disease is reported as extra-pulmonary TB (up to 47% of all TB cases in some settings). Due to limitations of the surveillance system, the epidemiology of Pott's disease and its treatment success are unknown. The Stop TB Strategy and Consolidated Action Plan to Prevent and Combat M/XDR-TB provide comprehensive roadmaps to address all types of TB.

Conclusions: The region needs to scale up implementation of effective strategies to curb TB and MDR-TB epidemics. There is a need to further analyze country data to document the extent of Pott's disease and develop specific guidelines for timely diagnosis and treatment of Pott's disease.

Keywords: Pott's disease, Extra-pulmonary tuberculosis, Multi-drug resistant tuberculosis, European Region, Action Plan

Introduction

The WHO European Region comprises 53 Member States and about 900 million population. Tuberculosis (TB) is a major public health in many countries of the Region. There is a wide variation in notification of TB from 2.8 (Italy) to 123 (Kazakhstan) per 100 000 population (Fig. 1). MDR-TB is a major challenge in the WHO European Region with, 29,000 MDR-TB cases occurred in the Region in 2010. MDR-TB among new and previously treated patients were 13.7% and 48.7%, respectively during the same year [1]. Extensively drug resistant (XDR) TB amounted 12.2% in 2010, although this may not be the true magnitude of XDR-TB because of the low coverage of anti-TB drug susceptibility testing for second-line anti-TB drugs, it is certainly expected to be more than 10%, as was also found in a previous study [2]. The percentage of HIV notified among all TB cases was 5.5% in 2010. In 2010, the treatment success rate among MDR-TB patients was 56.3% [1]. The high rates of MDR-TB combined with low-treatment outcomes and an increasing HIV epidemic pose an alarming treat to public health in the WHO European Region.

The trends in TB, drug resistant TB, TB/HIV coinfection with a focus on extrapulmonary TB in the region have not been previously documented. Furthermore, it is not clear whether there are differences in the rate of extrapulmonary TB across the various countries of the region. Just prior to this publication, the internationally recommended TB control strategy evolved from DOTS to the Stop TB strategy and yet the implication of the new strategy in terms of addressing all forms of the disease including extrapulmonary TB had not been previously discussed. In this paper, we thus address these knowledge gaps.

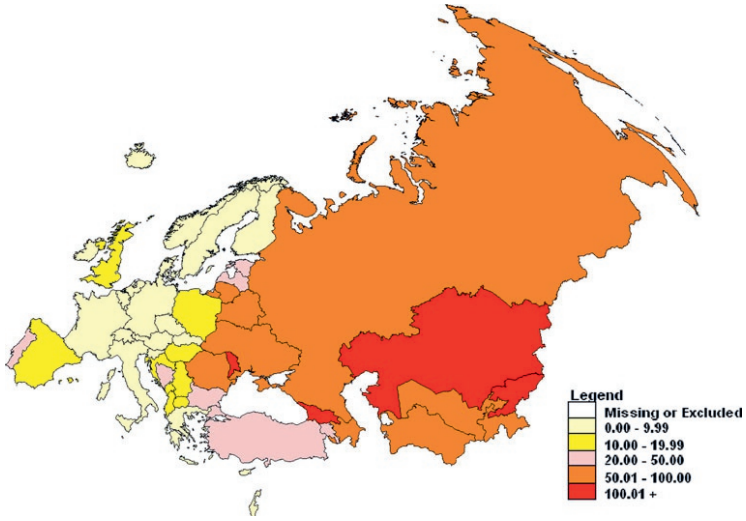

Figure 1. Notification rate of new and previously treated TB patients per 100,000 population, in the WHO European Region in 2010 [1]

In 1991, the World Health Assembly recommended that each National Tuberculosis Programme (NTP) work toward two objectives (the "WHO targets") by the year 2000: (1) to detect at least 70% of all sputum smear positive cases, and (2) to treat at least 85% of them successfully, by the introduction of an effective approach to TB control [3] which according to the "World Development Report 1993", is considered to be one of the most cost-effective health interventions [4]. As a combination of technical and managerial elements, DOTS proved to be effective making the infectious cases as non-infectious and breaking the cycle of transmission. In 1993, because of resurgence of TB globally, WHO took an unprecedented step and declared TB a global emergency. In 1994, after defining the nature and size of the global TB problem through expanded monitoring and surveillance, the International Union Against Tuberculosis and Lung Disease (The Union) and WHO promoted the technical and managerial approach suggested by Karel Styblo in the 1970s. In 1995, the strategy was packaged and branded as "Directly Observed Treatment Short course" (DOTS). The DOTS Strategy incorporating the fundamentals of TB control focused on a five-point policy package [3]:

1. Government commitment to sustained TB control;
2. Sputum smear microscopy to detect the infectious cases;
3. Standardized and directly observed short-course chemotherapy;
4. Uninterrupted supply of medicines;
5. Supervision, Monitoring and Evaluation.

During the period of 1995–2005, the emphasis was on piloting and expanding the DOTS Strategy. DOTS was widely accepted and adopted as a package of essential TB control measures, depending on the peculiarities of certain countries and local circumstances [5,6].

The number of countries using DOTS expanded from only 10 in 1990 to more than 180 in 2005, covering more than 80% of the world population [7]. After the collapse of the Soviet Union and mainly due to disruption of health services, TB re-emerged in the Region. In response, WHO and other partners scaled up their support for implementation and expansion of DOTS [6]. In 2002, the WHO/Europe Regional Committee endorsed the "DOTS expansion plan to Stop TB in the WHO European Region 2002–2006" [8, 9].

The DOTS Strategy has led to major progress in global TB control with successful treatment of nearly 20 million patients worldwide during 1995–2005 [8]. However, new challenges, such as the worsening of the HIV epidemic and rising of TB/HIV co-infection, emergence of drug-resistant strains TB and poor access of most vulnerable population, have proved that DOTS alone will not be sufficient for effective TB control [7, 9–11]. In 2006, WHO developed a new comprehensive strategy for TB control that consists of six components,

which builds on and goes beyond DOTS. This strategy addresses the spread of TB and HIV co-infections and MDR-TB [12]. Up to the time of this publication, this was a leading strategy for TB control worldwide, including in the European Region where the rates of M/XDR-TB are the highest in the world and HIV is spreading most rapidly [2, 13, 14].

The aim of the Stop TB Strategy is to dramatically reduce the global burden of TB, by halting the epidemic and reversing it by 2015, with the ultimate goal to eliminate TB as a public health problem by 2050. The aims, detailed objectives and targets of the strategy are summarized in Table 1. The six components of the Stop TB Strategy include to (1) pursue high-quality DOTS expansion and enhancement; (2) address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations; (3) contribute to health system strengthening based on primary health care; (4) engage all care providers; (5) empower people with TB, and communities through partnership; (6) enable and promote research. The implementation approaches of these components are listed in Table 2. DOTS as a five-point package remains the first component and foundation of the Stop TB Strategy. The other components of the Strategy highlight the need to address the challenge of drug-resistant TB and the co-epidemics of TB and HIV, the importance of engaging all care providers in TB care and control and of contributing to strengthening health systems, the role of communities and people with TB, and the fundamental role of research and development for new diagnostics, new drugs and new vaccines.

Table 1. The Stop TB Strategy at a glance

Vision	A TB-free world
Goal	To dramatically reduce the global burden of TB by 2015 in line with the Millennium Development Goals (MDGs) and the Stop TB Partnership targets
Objectives	• Achieve universal access to high-quality care for all people with TB • Reduce human suffering and socioeconomic burden associated with TB • Protect vulnerable populations from TB, TB/HIV and drug resistant TB • Support development of new tools and enable their timely and effective use • Protect and promote human rights in TB prevention, care and control
Targets	• MDG 6, Target 6.c: Halt and begin to reverse the incidence of TB by 2015 • By 2015 to reduce prevalence of and deaths due to TB by 50% compared with a baseline of 1990 • By 2050 to eliminate TB as a public health problem

Table 2. Six-components and implementation approaches of the Stop TB Strategy

1. Pursue high-quality DOTS expansion and enhancement
• Secure political commitment, with adequate and sustained financing • Ensure early case detection and diagnosis through quality assured bacteriology • Provide standardized treatment with supervision, and patient support • Ensure effective drug supply and management • Monitor and evaluate performance and impact
2. Address TB/HIV, MDR-TB and the needs of poor and vulnerable populations
• Scale-up collaborative TB/HIV activities • Scale-up prevention and management of multidrug-resistant TB (MDR-TB) • Address the needs of TB contacts and of poor and vulnerable populations
3. Contribute to health system strengthening based on primary health care
• Help improve health policies, human resource development, financing, supplies, service delivery and information • Strengthen infection control in health services, other congregate settings and households • Upgrade laboratory networks, and implement the practical approach to lung health • Adapt successful approaches from other fields and sectors, and foster action on the social determinants of health
4. Engage all care providers
• Involve all public, voluntary, corporate and private providers through public–private mix approaches • Promote use of the International Standards for Tuberculosis Care
5. Empower people with TB, and communities through partnership
• Pursue advocacy, communication and social mobilization • Foster community participation in TB care, prevention and health promotion • Promote use of the Patients' Charter for Tuberculosis Care
6. Enable and promote research
• Conduct programme-based operational research • Advocate for and participate in research to develop new diagnostics, drugs and vaccines

Methods

We analyzed the annual tuberculosis data submitted by the WHO European Region Member States and collected through the annual surveillance system jointly organized by the European Center for Disease Prevention and Control (ECDC) and the WHO Regional Office for Europe. The data included key variables which enable the countries and the WHO European Region to monitor the TB epidemiological situation, annual trends and outcomes of the national public health responses. The data were collected retrospectively from the cohorts of two years before each reporting cycle. This allows the countries to report the treatment outcomes of cohort of the patients and complete the required variables. Once the data was cleaned and validated. the results were presented descriptively using numbers and proportions. Maps were generated for the WHO region using Excel software and graded colors were used to express levels of measured outcomes. We analyzed each of the key epidemiological indicators including incidence, mortality, types of the disease (pulmonary and extrapulmonary TB), country of origin, as well as TB/HIV coinfection and

drug resistance rates. For the purposes of this study, we selected the data submitted in 2012 (the 2010 cohort of patients) and reviewed trends in the past five years.

We further reviewed the evolution of internationally recommended strategy from DOTS to the Stop TB strategy and discussed how the new strategy and the Regional Action Plan are to address the issue of extrapulmonary TB. Based on this study, we also identified the gaps in data which help strengthen surveillance system and analyzed in the future studies.

Results

Comparing the key TB indicators between 2005 to 2010 showed that notification of all cases decreased from 54 cases in 100,000 population [15] to 34 in 100,000 population [1]. This is while the percentage of MDR-TB among all TB cases had been increasing over the period from 4.3% to 7.5%. Likewise, the percentage of HIV notified among all TB cases increased from 3.4% which is the first year with regional representative data to 5.5% in 2010. Over the last 5 years treatment success rates have continued to decrease, falling from 72.5% and 50% in 2005 to 68.7% and 47.6% in 2010 among new and previously treated cases, respectively (table 3).

Table 3. Trends in key TB indicators 2005-2010

Indicator	2005	2010
Tuberculosis notification per 100,000 population	54	34
Multi-drug resistant TB rate among all TB patients	4.3%	7.5%
TB/HIV coinfection	No representative data*	5.5%
Extrapulmonary TB among all TB patients	12%	17%
Treatment success among new TB patients	72.5%	68.7%
Treatment success among retreatment TB patients	50%	47.6%

3.4% (the first comprehensive data available in 2008)

In 2010, among the 388,875 notified TB cases in the WHO European Region, 65,783 (17%) cases had extra-pulmonary TB [1]. Most countries have reported less than 1% of cases with unknown disease localization (Table 4). Only Turkmenistan, Bosnia and Herzegovina and Denmark still need to improve their notification by disease localization; these countries reported 8.5%, 11.4%, and 18.1% cases with unknown site of disease, respectively. On average, in the European Union/ European Economic Area (EU/EEA) countries, a higher proportion of extra-pulmonary localization of the disease among all TB cases was observed than in non-EU/EEA countries; 22% versus 16% (Fig. 2). Five countries reported more than 40% of extra-pulmonary TB cases: The United Kingdom (47%), the Netherlands (45%), Andorra (43%), Norway and Malta (41% each) [1]. Our analysis also showed that the percentage of extrapulmonary forms among all TB patients increased from 12% in 2005 to 17% in 2010.

Table 4. Notified tuberculosis cases by site of diseases, WHO European region 2010

Country	Pulmonary										
	Pulmonary only		Pulmonary + extrapulmonary		Total pulmonary		Extrapulmonary		No site reported		Total
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
EU/EEA											
Austria	497	72.2	60	8.7	557	81	131	19	0	0	688
Belgium	733	65.7	74	6.6	807	72.4	307	27.5	1	0.1	1 115
Bulgaria	1 762	66.5	89	3.4	1 851	69.9	798	30.1	0	0	2 649
Cyprus	40	65.6	0	0	40	65.6	19	31.1	2	3.3	61
Czech Republic	560	82.6	21	3.1	581	85.7	97	14.3	0	0	678
Denmark	227	63.2	24	6.7	251	69.9	43	12	65	18.1	359
Estonia	264	80.2	44	13.4	308	93.6	21	6.4	0	0	329
Finland	241	73.7	-	-	241	73.7	86	26.3	0	0	327
France	3 017	59	702	13.7	3 719	72.7	1 361	26.6	36	0.7	5 116
Germany	2 879	66.5	435	10	3 314	76.5	980	22.6	36	0.8	4 330
Greece	361	73.8	59	12.1	420	85.9	69	14.1	0	0	489
Hungary	1 642	94.3	25	1.4	1 667	95.7	74	4.3	0	0	1 741
Iceland	11	50	7	31.8	18	81.8	4	18.2	0	0	22
Ireland	251	58.8	23	5.4	274	64.2	150	35.1	3	0.7	427
Italy	2 423	74.6	262	8.1	2 685	82.6	564	17.4	0	0	3 249
Latvia	788	84.4	58	6.2	846	90.6	88	9.4	0	0	934
Lithuania	1 713	88.4	-	-	1 713	88.4	225	11.6	0	0	1 938
Luxembourg	23	79.3	-	-	23	79.3	6	20.7	0	0	29
Malta	10	31.3	9	28.1	19	59.4	13	40.6	0	0	32
Netherlands	458	42.7	128	11.9	586	54.6	482	44.9	5	0.5	1 073
Norway	153	45.1	48	14.2	201	59.3	138	40.7	0	0	339
Poland	6 949	92.5	43	0.6	6 992	93.1	517	6.9	0	0	7 509
Portugal	1 732	66	149	5.7	1 881	71.6	727	27.7	18	0.7	2 626
Romania	16 708	79.3	1 300	6.2	18 008	85.4	3 070	14.6	0	0	21 078
Slovakia	337	76.8	35	8	372	84.7	67	15.3	0	0	439
Slovenia	117	68	25	14.5	142	82.6	30	17.4	0	0	172
Spain	5 238	73.9	-	-	5 238	73.9	1 851	26.1	0	0	7 089
Sweden	342	50.7	77	11.4	419	62.1	256	37.9	0	0	675
United Kingdom	3 606	42.5	882	10.4	4 488	52.9	3 949	46.6	46	0.5	8 483
Subtotal EU/EEA	**53 082**	**71.7**	**4 579**	**6.2**	**57 661**	**77.9**	**16 123**	**21.8**	**212**	**0.3**	**73 996**
Non-EU/EEA											
Albania	-	-	-	-	275	61.8	170	38.2	0	0	445
Andorra	-	-	-	-	4	57.1	3	42.9	0	0	7
Armenia	-	-	-	-	1 090	61.2	690	38.8	0	0	1 780
Azerbaijan	-	-	-	-	7 274	86.7	1 120	13.3	0	0	8 394
Belarus	-	-	-	-	5 107	92	447	8	0	0	5 554
Bosnia and Herzegovina	-	-	-	-	1 067	76.8	164	11.8	159	11.4	1 390
Croatia	-	-	-	-	608	87.5	87	12.5	0	0	695
Georgia	-	-	-	-	3 748	64.7	2 048	35.3	0	0	5 796
Israel	-	-	-	-	269	78.4	74	21.6	0	0	343
Kazakhstan	-	-	-	-	22 614	79.2	5 936	20.8	0	0	28 550
Kyrgyzstan	-	-	-	-	4 660	74	1 635	26	0	0	6 295
North Macedonia	-	-	-	-	309	73.6	111	26.4	0	0	420
Moldova	-	-	-	-	4 934	90.6	513	9.4	0	0	5 447
Monaco	-	-	-	-	0	0	1	100	0	0	1

Montenegro	-	-	-	-	100	87.7	14	12.3	0	0	114
Russia	-	-	-	-	145 858	89.7	16 695	10.3	0	0	162 553
San Marino	-	-	-	-	-	-	-	-	-	-	-
Serbia	-	-	-	-	1 871	78.4	514	21.6	0	0	2 385
Serbia excluding UN Administered Province of kosovo	-	-	-	-	1 286	85.7	215	14.3	0	0	1 501
UN Administered Province of kosovo	-	-	-	-	585	66.2	299	33.8	0	0	884
Switzerland	-	-	-	-	366	66.7	183	33.3	0	0	549
Tajikistan	-	-	-	-	4 985	65.2	2 656	34.8	0	0	7 641
Turkey	-	-	-	-	10 740	64.9	5 811	35.1	0	0	16 551
Turkmenistan	-	-	-	-	2 483	76.9	473	14.6	274	8.5	3 230
Ukraine	-	-	-	-	32 405	89	3 639	10	365	1	36 409
Uzbekistan	-	-	-	-	13 654	67.2	6 676	32.8	0	0	20 330
Subotal non-EU/ EEA	**-**	**-**	**-**	**-**	**264 421**	**84**	**49 660**	**15.8**	**798**	**0.3**	**314 879**
Total European Region	**-**	**-**	**-**	**-**	**322 082**	**82.8**	**65 783**	**16.9**	**1 010**	**0.3**	**388 875**
Subtotal 18 HPC	**-**	**-**	**-**	**-**	**282 278**	**84.1**	**52 541**	**15.7**	**639**	**0.2**	**335 458**

Only for EU/EEA countries anti-TB drug resistance was recorded by site of disease. Among all 31 644 cases with drug susceptibility available in EU/EEA countries, 6 933 were from extra-pulmonary TB cases. The rate of MDR-TB among extra-pulmonary TB cases with drug susceptibility available was 2.3% (n = 158). This rate was lower than the rate of 5.2% MDR-TB among pulmonary TB cases (n = 1 289).

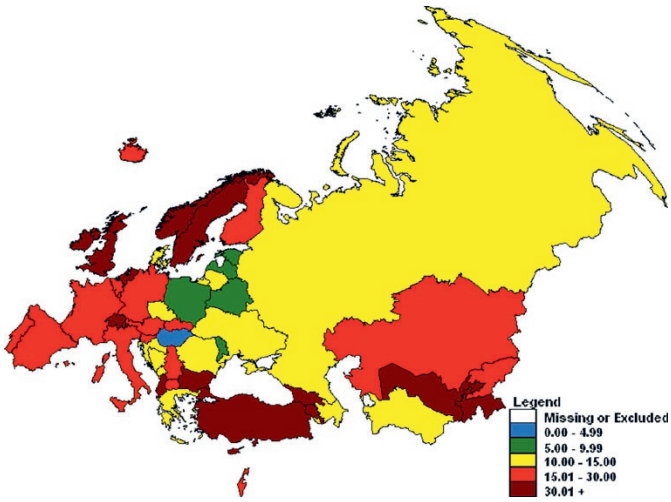

Figure 2. Percentage of extrapulmonary tuberculosis reported in the WHO European Region in 2010

Discussion

TB is still causing a considerable health burden in the WHO European Region, with increasing MDR-TB rates. The proportion of extra-pulmonary cases has remained relatively stable over the last 4 years. Pott's disease is reported together with other extra-pulmonary TB cases to the joint WHO/ECDC surveillance system and as a result, the exact magnitude of the disease is unknown. The variances in the reporting of extra-pulmonary TB may result from different diagnostic practices across the region or epidemiological factors, such as immigration or the prevailing M. tuberculosis strains [16].

M/XDR-TB is a man-made phenomenon that emerges as a result of inadequate treatment of tuberculosis and/or poor airborne infection control in health care facilities and congregate settings. The spread of M/XDR TB is also an indication to low adherence to evidence-based TB control practices [2, 13, 14, 21, 22].

The reasons for lower rate of MDR-TB among extrapulmonary TB with available drug susceptibility testing can be due to variety of reasons including quality of samples, the limitation of the diagnostic tools used and the more frequent occurrence of extrapulmonary forms among patients coming from countries out of the region. The reasons for increase in the rate extrapulmonary among all TB patients needs further investigation but could be due to changes in migration patterns and/or improvement in diagnosis. Due to limited data on variables specific to disease localization, further analysis of extra-pulmonary disease such as HIV status or treatment outcomes are not available. Therefore, there is a need to improve surveillance and/or conduct surveys to get a better understanding of extrapulmonary TB, the extent of Pott's disease and the reasons for the wide variation of the proportion of extrapulmonary TB among all TB cases across the Region. These findings call for inclusion of more indicators and their timely reporting.

Evidence-based data suggest that improved diagnosis and treatment based on the Stop TB Strategy have already saved millions of lives globally [17]. The decline of TB incidence is < 1% per year and the long-term elimination target, to reduce incidence to less than one case per million by 2050, will not be reached with existing technologies and approaches [10, 11]. Trend analysis of the MDG targets in 2010 showed that estimated prevalence in the European Region has been declining, but not enough to be able to reach the MDG6 target by the 2015 deadline. Estimated mortality from TB decreased to 6.8 per 100,000 population in 2010. To meet the MDG 6 target, TB mortality must further decline to 6.5 per 100 000 population by 2015 [16]. The WHO Regional Office for Europe held the WHO European Ministerial Forum "All against Tuberculosis" on 22 October 2007 in Berlin, Germany [18], to accelerate progress towards achieving the MDG's targets for TB control in the WHO European Region. The main outcome of the Forum was the adoption of the Berlin Declaration on TB as well as endorsement of the two Regional plans: the WHO/

Europe Plan to Stop TB in 18 High-priority countries in the WHO European Region 2007–2015 and ECDC Framework Action Plan to fight tuberculosis in the European Union [19, 20]. The Forum and the Declaration in particular renewed commitments to take actions to control TB in the European Region highlighting that: (1) TB, and MDR-TB in particular, is a health security threat; (2) Strengthening political and financial commitment is vital to reach the MDGs and (3) to establish adequate fora and mechanisms to assess progress at regional level [19].

WHO Regional Office for Europe, in collaboration with technical agencies, Member States, civil society organizations and communities, developed a Consolidated Action Plan to Prevent and Combat M/XDR-TB in WHO European Region 2011–2015. The Consolidated Action plan and its accompanying resolution EUR/RC61/R7 were fully endorsed at the sixty-first session of the WHO Regional Committee for Europe in Baku, Azerbaijan in September 2011 [23]. The plan emphasizes on strengthening the quality of implementation of the Stop TB Strategy, in particular the essential elements of TB control, such as early detection and notification of all TB cases as well as supervised treatment avoiding the misuse of anti-TB drugs [23]. The plan calls for accelerated action, working in close partnership with member states and all partners, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria and the Stop TB Partnership. The goal of the plan is to contain the spread of drug-resistant TB by achieving universal access to prevention, diagnosis and treatment of M/XDRTB in all member states in the WHO European Region by 2015. The targets of the plan are to diagnose at least 85% of all estimated MDR-TB patients, treat successfully at least 75% of all patients notified as having MDR-TB and to decrease by 20% points the proportion of MDR-TB among previously treated patients [23].

The Consolidated Action plan to prevent and combat M/XDR-TB comprises six strategic directions and seven areas of intervention. The strategic directions are crosscutting and are designed to safeguard the values of the Health 2020 strategy. These include: (1) identifying and addressing determinants and underlying risk factors contributing to the emergence and spread of drug-resistant TB; (2) strengthening the health system response in providing accessible, affordable and acceptable services using patient-centered approaches; (3) working in national, regional and international partnerships on TB prevention, control and care; (4) fostering regional and international collaboration for development of new diagnostic tools, medicines and vaccines against TB; (5) promoting rational use of existing resources, identifying gaps and mobilizing additional resources to fill the gaps; (6) monitoring the trends of M/XDR-TB in the Region and measuring the impact of interventions. The areas of intervention are in line with the Global Plan to Stop TB 2011–2015 and include the same targets as set by the Global Plan and World Health Assembly resolution WHA62.15, namely to provide universal access to diagnosis and treatment of MDR-TB: (1) prevent the development of M/XDR-TB cases; (2) scale up access

to testing for resistance to first- and second-line anti-TB drugs and to HIV testing and counseling among TB patients; (3) scale up access to effective treatment of drug-resistant TB; (4) scale up TB infection control; (5) strengthen surveillance, including recording and reporting, of drug-resistant TB; (6) expand country capacity to scale up the management of drug-resistant TB, including advocacy, partnership and policy guidance; (7) address the needs of special populations. The action plan clearly defines milestones and a detailed set of recommended activities. Furthermore, a monitoring framework was developed to track progress toward milestones and the eventual achievement of objectives. If the Plan is fully implemented, 225,000 MDR-TB patients will be detected and 127,000 of them will be successfully treated. As a result of successful implementation of the Plan, 250,000 MDR-TB and 13,000 XDR-TB cases would be averted and 120,000 lives will be saved. The direct economic gain in lives saved by the Plan amounts to US$ 5 billion over the 5 years. In addition, US$ 7 billion will be saved directly on costs for detection and care of the M/XDR-TB cases averted, which would have arisen and needed treatment in the absence of improved TB control provisions of the plan. Its implementation will also have an impact on preventing transmission, and thus averting many more MDR-TB cases beyond 2015 that are as yet undetermined but will go far beyond this number.

To address the lack of international consensus on the role of surgery in pulmonary and extrapulmonary TB including tuberculosis spondylitis, the plan foresees that the WHO Regional Office in collaboration with the Member States and other partners develop a set of evidence-based criteria for surgery for M/XDR-TB patients by the end of 2012.

It is known that TB is a social disease and it is seen frequently in stigmatized and vulnerable groups such as the poor, migrants, drug abusers, prisoners. Further work is need to these groups, addressing social determinants, ethical values and human rights in collaboration with other programmes within WHO as well as national and international partners [10, 11].

Countries need to urgently scale up the implementation of the Stop TB Strategy, ensuring early diagnosis and proper treatment, strengthening health-system policies, establishment of links with the broad economic and health reforms, including addressing social determinants of TB, and promotion of research efforts, including the development of new diagnostics, anti-TB drugs and vaccines. Adequate interventions addressing drug-resistant TB require proper national planning and effective implementation of comprehensive approaches with the support from national and international partners. Further research on optimal treatment and care for Pott's disease is needed.

Conflict of interest None.

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CHAPTER 3

3

Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-resistant Tuberculosis in the WHO European Region 2011 – 2015: cost-effectiveness analysis

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Abstract

Drug-resistant tuberculosis (TB) has increased at an alarming rate in the WHO European Region. Of the 27 countries worldwide with a high burden of multidrug resistant-TB (MDR-TB), 15 are in the European Region. An estimated 78,000 new cases of MDR-TB occur annually in the Region, of which approximately 10% are extensively drug-resistant (XDR)-TB. In response, the WHO Regional Office for Europe developed a Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-resistant Tuberculosis (2011–2015). Our objective was to analyse the cost-effectiveness of implementing the plan, with the expected achievements of diagnosing 85% of estimated MDR-TB cases and treating at least 75% successfully. A transmission model, using epidemiological data reported to WHO was developed to calculate expected achievements. WHO-CHOICE database was used for cost analyses. The highly cost-effective plan is expected to prevent the emergence of 250,000 new MDR-TB and 13,000 XDR-TB patients respectively, saving US$7 billion and 120,000 lives. The plan and accompanying Resolution were fully endorsed by the sixty-first session of the WHO Regional Committee for Europe in 2011. Member States need to continuously improve health system performance and address TB determinants. Research and development of new medicines, tools and patient-friendly services are also crucial.

Key words: multidrug resistant-TB, extensively drug-resistant-TB, WHO European Region

1. Introduction

In Europe, tuberculosis (TB) is commonly regarded as a disease of the past. However, as the threat of antimicrobial resistance has become a global reality in recent years, one of the most alarming examples has become the frequency of multidrug- and extensively drug-resistant TB (M/XDR-TB). The WHO European Region currently has the highest proportion of M/XDR-TB patients, and 15 out of the world's 27 high M/XDR-TB burden countries, in the world.[1] Effective treatment for MDR-TB can take up to two years (even longer for XDR-TB) and is often associated with debilitating side effects.

Although encouragingly the rates of new TB cases in the Region have been falling since 2005, a look at the epidemiological situation of M/XDR-TB reveals a daunting picture. In 2011, there were an estimated 78,000 cases of MDR-TB (in the Region), of which 29,473 (38%) were detected.[2] This accounts for one-fourth of all estimated and more than half of all notified MDR-TB cases globally.[1] The proportion of MDR-TB amongst newly notified TB cases and previously treated cases was 14% and 47% respectively,[2] with rates reaching significantly higher in some countries.[3] XDR-TB is estimated to account for 10% of all MDR-TB cases.[2] The number of countries reporting XDR-TB cases also continues to increase. Over 40% of all mortality from communicable diseases in the WHO European Region is attributed to TB, largely due to the prevalence of M/XDR-TB; in 2011, 44,000 people in the European Region died of TB.[2] In addition to the human cost of severe illness and death, the prevalence of M/XDR-TB poses an enormous economic burden in areas that are the most resource limited.

In 2011, in consultation with Member States, civil society organizations and stake holders including patients' representatives, a Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-resistant Tuberculosis (2011–2015) was developed by the WHO Regional Office for Europe for all 53 Member States. The goal of the Plan is to contain the spread of drug-resistant TB by achieving universal access to prevention, diagnosis and treatment of M/XDR-TB in all member states in the WHO European Region by 2015.[3] The Plan has six strategic directions and seven areas of intervention, which are aligned with the Global Plan to Stop TB 2011–2015. The specific targets to be met by the end of 2015 are to: decrease by 20% the proportion of MDR-TB amongst retreatment patients, diagnose at least 85% of all estimated MDR-TB patients, and successfully treat at least 75% of all patients notified of having MDR-TB.

Successful treatment and lives saved have a direct economic benefit in countries most affected by M/XDR-TB. The objective of this study was to analyse the cost-effectiveness of implementing the Plan, with its expected targets achieved.

2. Methods

The WHO Regional Office for Europe commissioned the Royal Tropical Institute in Amsterdam to estimate the costs for implementation of the Consolidated Action Plan to Prevent and Combat M/XDR-TB 2011–2015, on the basis of the expected achievements and benefits of implementing the Plan. The study was a collaboration between the Royal Tropical Institute in the Netherlands, the WHO Regional Office for Europe and WHO headquarters. The findings and methodology were peer-reviewed by experts at Imperial College in London, United Kingdom.

The costing methods are described in detail in Annex 4 of the Action Plan.[3] In brief, a cost model was created using the public health system perspective for budgeting and unit cost calculation taking into account the targets for detection and treatment of M/XDR-TB patients defined in the Action Plan. Direct costs incurred by the public health care system, and costs for stewardship, supervision and capacity-building were included in the model. Indirect costs incurred by patients and society were excluded from the model. The estimated number of MDR-TB and XDR-TB patients, number of patients screened for M/XDR-TB, and the number of patients treated for M/XDR-TB from 2011–2015 were based on linear projections of the most recent epidemiological data (from 2007–2009 at the time of the study).

Cost and epidemiological data were sourced from the WHO Regional Office for Europe, European Centre for Disease Prevention and Control (ECDC), the Foundation for Innovative New Diagnostics (FIND), Joint United Nations Programme on HIV/AIDS (UNAIDS) and academic publications. Budgets were formulated by including the complete treatment costs of all M/XDR-TB patients envisaged to be enrolled in 2011–2015, including treatment for those cases beyond 2015. Budgets were prepared for the 18 high-priority countries (HPC) and 35 non-HPC separately because the incidence of M/XDR-TB and unit costs varied significantly between the two groups. The 18 HPC are: Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Republic of Moldova, Romania, Russian Federation, Tajikistan, Turkey, Turkmenistan, Ukraine, and Uzbekistan. As per standard practice, a discount rate of 0.03 was chosen in estimating the budget and unit costs.[4]

Unit costs: The cost of equipment was calculated assuming a 10-year life cycle of costs and throughput and a discount rate of 0.03. The annual maintenance costs of equipment were fixed at 5% of the total cost of equipment at delivery, except for the Xpert MTB/RIF assay, for which FIND has a fixed annual maintenance cost of 8%.[5] In order to account for excess capacity an idle rate of 10% for all equipment was considered. The cost of staff time was based on annual expenditure and throughput. The total amount of staff time available for a year was calculated assuming a standard work schedule of 8 hours per day, 22 days per month and 11 months per year. Excess staff capacity was estimated at 15%. Staff salaries for diagnostics were obtained from the WHO-CHOICE database using 2005 values for the

Health Worker category.[6] Euro A values were used for non-HPC. The average of Euro B and Euro C values was used for HPC. The costs of materials were allocated directly. A wastage rate of 5% was considered for consumables. As per the WHO-CHOICE database, the cost of delivery of diagnostic tests and equipment was 20% of the free on board cost.[7] The costs of materials, consumables and equipment as well as the unit cost of a chest X-ray were retrieved from the planning and budgeting tool for TB control activities.[8]

The unit cost of M/XDR-TB treatment was calculated for a regimen comprising 6 months of intensive treatment and 18 months of continuation treatment at a dosage recommended for a person of average size (60 kg) according to WHO guidelines. The costs of diagnostics were based on the average number of laboratory tests a patient would undergo during the standard length of treatment. The cost of ambulatory care was based on the average number of outpatient visits during the standard length of treatment. The average cost for a ten-minute outpatient visit, assuming 50% population coverage, was calculated according to the WHO-CHOICE database.[6] The cost of inpatient care was based on the percentage of patients hospitalized and the average annual length of stay. In line with the aim of the Action Plan to improve models of care and promote patient-centred approaches, it was estimated that MDR-TB patients would be hospitalized for three months and XDR-TB patients for one year, and that 80% of patients in HPC and non-HPC would be hospitalized.[9] Since MDR-TB patients require sophisticated medical interventions and facilities such as negative pressure ventilation rooms, the average cost of a secondary care hospital day was used for the calculation of inpatient costs. The cost of therapeutics and diagnostics for the management of side-effects and care for M/XDR-TB patients during inpatient stays was estimated at 31% of the total inpatient cost.[10] For both ambulatory and inpatient unit costs, Euro A costs were used for non-HPC and the average of Euro B and Euro C costs for HPC.

Modelling for calculation of expected achievements: Expected achievements of the Action Plan were based on the targets for detection and treatment of M/XDR-TB patients as defined in the Plan. To estimate the number of M/XDR-TB cases that could be averted in the Region the model of direct transmission of TB over the duration of the Plan was applied, thus excluding possible averted transmission from secondary and tertiary cases. Based on the Styblo model, it was assumed that each untreated sputum smear-positive patient could lead to 1.25 new TB cases over one transmission cycle.[11]

The estimated number of averted cases was calculated by subtracting the number of patients who are successfully treated or died under treatment from the number of patients who are spontaneously cured or died without any intervention. The number of M/XDR-TB cases that cure spontaneously was assumed to be 5% and the case fatality rate without intervention was assumed to be 30%.[12] The number of averted cases was calculated separately for MDR-TB and XDR-TB cases. The percentage of successfully treated MDR-TB

patients used was assumed to be the same as reported by WHO for 2009 (57.4%) and then linearly increased to reach the target of 75% in 2015, and the TB fatality rate amongst detected cases and under treatment was assumed to be 10.1%, the same as recorded in 2009,[13] and to remain stable for 2011–2015. In order to calculate XDR-TB cases averted it was assumed that the number of XDR-TB cases would remain at 10% of MDR-TB cases[14] and that the treatment success and death rates amongst detected XDR-TB were 51% and 20%, respectively. Data on treatment success and death rates for XDR-TB cases are sparse, therefore an average of the rates reported in four scientific publications were used.[15-18]

The number of lives saved through implementation of the Action Plan was calculated as the difference between the projected number of MDR-TB deaths (mortality rate of MDR-TB patients under treatment multiplied by the number of MDR-TB cases) and the estimated number of TB deaths in the scenario that the Action Plan was not implemented and the TB epidemic continued.

Cost-effectiveness: The cost per disability-adjusted life-year (DALY) gained was calculated by dividing the cost per death averted by the average of DALYs gained per death averted.[19] An average of 21 DALYs gained per death averted was used as a conservative estimate.[7] The cost per death averted amounted to the total budget divided by the number of deaths averted. The cost per DALY gained was determined by dividing cost per death averted by the average of DALYs gained per death averted. Cost–efficiency was determined by comparing the cost per DALY weighted by the estimated number of MDR-TB cases based on the average GDP (2011 figures), weighted by the respective country populations.

Economic gain: Multiplication of GDP per capita and DALYs gained comprises the long-term direct economic gain of the lives saved over the period 2011–2015. The DALYs gained per deaths averted was determined by multiplication of the number of lives saved by the average of DALYs gained per live saved. The short-term direct economic gain up to 2015 was limited to the DALYs gained within the time frame of the Plan. Additional indirect short-term gain was restricted to the savings from the cost of treatment of M/XDR-TB cases averted by implementation of the Plan up to 2015 (direct transmission events). To calculate these treatment costs, a treatment unit cost was derived from the total budget by dividing it by the number of cases enrolled in treatment. The long-term indirect gain from averting cases by stopping the chain of transmission was not determined, as this requires more detailed epidemiological transmission modelling. A resources availability assessment and the assumptions for a resource availability forecast are further discussed in detail in Annex 4 of the Action Plan.

3. Results

Epidemiological modelling indicates that 225,000 cases of MDR-TB will be detected out of a total of 367,000 projected cases of MDR-TB through implementation of the Action Plan

between 2011 and 2015. Approximately 127,000 cases are expected to be successfully treated during the five-year period, and 200,000 MDR-TB patients are expected to be enrolled in treatment. The expected trends in MDR-TB incidence, case detection, treatment enrollment and treatment success are shown in Figure 1. Consistent with current trends, 99% of the total detected MDR-TB patients in the WHO European Region are expected to be found in the HPC. With the implementation of the Action Plan, 250,000 cases of MDR-TB and 13,000 XDR-TB cases are expected to be averted, and 120,000 lives are expected to be directly saved in the short-term.

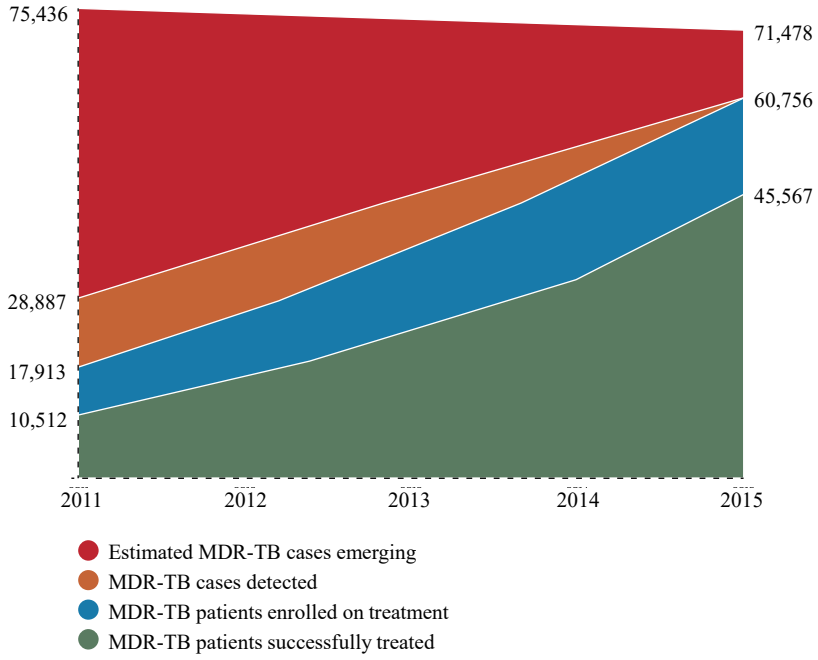

Figure 1. Expected trends with the implementation of the Action Plan, 2011–2015

Costs: When the M/XDR-TB costing tool was applied to the epidemiological model, it was found that implementation of the Action Plan would cost US$ 5.2 billion, with an annual budget range between US$ 453 million for 2011 and US$ 1.7 billion for 2015. This includes treatment completion of the cohort of 2015 M/XDR-TB patients. HPC are estimated to account for approximately 96% of the total financing. The resources required according to budget item are shown in Table 1.

The direct cost of treating an MDR-TB patient undergoing a standard treatment cycle of 24 months was calculated to be US$ 25,400 in HPC and US$ 56,300 in non-HPC. Inpatient treatment represented 43% and 68% of the treatment cost for MDR-TB and XDR-TB cases, respectively. The Xpert MTB/RIF assay appeared to be the least expensive diagnostic tool

for the screening of first-line anti-TB drug resistance. This assay incurs a cost of US$ 24.1 and US$ 71.7 per screened patient in HPC and non-HPC, respectively. The least expensive diagnostic test for second-line DST was solid media culture. Solid media DST costs US$ 46.6 and US$ 62.2 per drug in HPC and non-HPC, respectively.

Table 1. Resources required according to budget item per year of the Action Plan, 2011–2015 (US$ million and in percentage).

Budget item	2011	2012	2013	2014	2015	Total *	%
Drugs	91	142	203	276	360	1,072	21
Diagnostics	74	104	138	177	221	713	14
Ambulatory care	101	156	223	302	394	1,177	23
Inpatient care	155	250	367	505	667	1,943	38
Patient support costs	16	24	34	47	61	181	4
Additional costs for HIV treatment	2	3	4	5	7	20	<1
Stewardship expenditure	15	15	15	15	15	73	1
Total	454	694	984	1,327	1,725	5,179	100

* Yearly amounts have been rounded for ease of interpretation, and therefore do not always equal the five-year period totals.

Cost-effectiveness and Economic gain: An overview of the cost-effectiveness and economic gain from the Plan is shown in Table 2. Comparison of the costs per DALY gained with GDP per capita showed that the intervention was highly cost-effective. The direct economic gain from saving 120,000 lives amounted to US$ 5 billion in the short term (DALYs gained up to 2015) and US$ 48 billion in the long term. The short-term indirect economic gain from averting 263,000 M/XDR-TB cases amounted to about US$ 6.9 billion. The long-term economic indirect gain has not been determined, but will be far greater than the short-term amount because many future transmission events were not considered in this study.

4. Discussion

Results of this study show that interventions described in the Action Plan are highly cost-effective. Implementation of the Action Plan in 2011–2015 in the WHO European Region would prevent of the emergence of 250,000 new MDR-TB and 13,000 XDR-TB cases respectively, saving nearly US$7 billion and 120,000 lives in the short-term. This study also found that implementation of the Action Plan was highly cost-efficient with an average cost of US$ 2044 per DALY gained versus an average GDP per capita of US$ 24,346 in the Region.

It is important to note that these findings represent benefits that are restricted to predicted transmission events within the five-year time frame of the Plan and are thus an underestimation of its overall (future) benefits. Health system changes, for example

in criteria for hospitalization and adaptation of models of care with treatment in ambulatory services, day-care centres and home-/community-based treatment rather than hospitalization have the potential to decrease costs significantly. In addition, there are likely to be long-term benefits of addressing social determinants related to M/XDR-TB, which is an important component of the Plan.

Table 2. Overview of the cost-effectiveness and economic gain from the Action Plan, 2011–2015

		WHO European Region	HPC	Non-HPC
Overview of the cost-effective analysis of the Action Plan	Number of lives saved	120,105	119,220	885
	Budget of the Plan (US$ million)	5,179*	4,970	135
	Cost per death averted (US$)	42,916	41,502	149,647
	Average of DALYs gained per death averted (years)	21	21	21
	Costs per DALY gained (US$)	2,044	1,976	7,126
	GDP per capita (US$)	24,346	13,851	32,348
	Assessment results	very cost-effective	very cost-effective	very cost-effective
Economic gain from lives saved 2011–2015 by implementation of the Plan (short-term direct impact)	Number of lives saved	120,105	119,220	885
	Average of DALYs gained per life saved (years)	5	5	5
	DALYs gained per deaths averted (years)	275,569	272,359	3,210
	GDP per capita (US$)	32,887	18,699	43,704
	Gain (US$ million)	5,233	5,092	140
Economic gain from lives saved 2011–2015 by implementation of the Plan (long-term direct impact)	Number of lives saved	120,105	119,220	885
	Average of DALYs gained per life saved (years)	21	21	21
	DALYs gained per deaths averted (years)	2,522,195	2,503,609	18,586
	GDP per capita (US$)	32,887	18,699	43,704
	Gain (US$ million)	47,628	46,815	812
Economic gain from M/XDR-TB cases averted up to 2015 by implementation of the Plan (short-term indirect impact)	Budget of the Plan (US$ million)	5,179*	4,970	135
	Number of M/XDR-TB patients put on treatment	198,898	197,600	1,298
	Unit cost per M/XDR-TB patient care (US$)	26,038	25,156	104,377
	Number of M/XDR-TB cases averted	263,442	260,767	2,675
	Gain (US$ million)	6,838	6,559	279

* Regional budget amount does not equal to the sum of HPC and non-HPC amounts due to rounding in the Regional budget model.

The Consolidated Action Plan comprises a comprehensive and integrated approach to controlling the problem of M/XDR-TB in the Region with an extensive monitoring framework and key indicators.[3,20] There are 11 core (key) indicators, for which data is collected and measured annually, and that allow for the monitoring of performance in the main areas and interventions in the Action Plan. These 11 core indicators are part of a comprehensive full set of indicators that correspond to the seven areas of intervention of the Action Plan, and for which data has and will continue to be collected throughout the five-year period of the Plan. The WHO Regional Office for Europe has just completed a full study of the indicators of the Action Plan for all 53 Member States in the Region in 2011-2013. Forthcoming results of that study will give a key indication of the progress since the implementation of the Action Plan and challenges that remain to be addressed. In addition, this study will allow for further monitoring of the cost-effectiveness of the Plan.

Strengths and limitations: This study represents a rigorous and robust cost-effectiveness analysis that utilized the latest epidemiological and cost data from the Region. As a measure of the reliability of this study, results were within rage of those found in other studies. For example, Diel and colleagues recently calculated the average cost of treatment of MDR-TB amongst old European Union (EU)-15 countries, plus Cyprus, Malta and Slovenia to be €57,213 and €24,166 for M/XDR-TB in new EU states.[21] White and Moore-Gillon previously estimated the mean direct cost of managing an MDR-TB patient in the United Kingdom to be £60,000,[22] and Rajbhandary and colleagues estimated the mean direct cost of treating an MDR-TB patient in the United States to be US$ 45,000.[10]

This study, however, was limited by availability of data. Laboratory management costs and specimen transport costs were not included due to lack of data and are likely to vary widely between countries. Owing to the high variation of criteria availability and cost in the countries, the cost of surgery (which is normally performed on 2–5% of M/XDR-TB patients) was not considered. The costs of active contact-tracing and testing of contacts were also excluded. The budget and unit cost estimates are prone to changes in efficiencies of screening and treating M/XDR-TB patients, variations in inpatient care as well as epidemiological trends in M/XDR-TB. There were also limitations imposed by the absence of extended transmission dynamics modelling; neither the number of lives that would be saved amongst those cases averted by the Plan, nor the number of lives that would be saved by the prevention of transmission by these averted and successfully treated cases were included. Other limitations on the calculation of the expected epidemiological achievements include: that no account was taken of the fact that M/XDR-TB cases are also averted by improved interventions for drug-susceptible and mono-resistant TB cases, and that consideration was not given to delays in detection or treatment because of the absence of data on these variables.

Conclusions and future perspectives: This study demonstrates that the Consolidated Action Plan is a cost-effective answer to the threat of M/XDR-TB in the Region. These results are not only relevant to the short-term future – In the long-term from a regional and global perspective, M/XDR-TB if left uncontrolled has the potential to impose a post-antibiotic era,[23] which will be hundreds of times more costly to tackle. Currently, there is a considerable projected funding gap of over 60% in order to fully implement the Plan. In countries supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria, 78% of M/XDR-TB patients are successfully treated compared to 20% in other settings. This is powerful evidence that mobilization of substantial funding from Global Fund, other international donors and national resources can make the difference in reaching the goals of the Action Plan. The current economic climate has placed an even greater burden on the social determinants of M/XDR-TB. There is a great need, therefore, to invest in health systems that place emphasis on patient-centred models of care that are in line with the WHO Action Plan and the European policy framework, Health 2020. The costs associated with these changes not only have immeasurable life-saving benefits, but also strategic short-term and long-term economic benefits that we cannot afford to overlook.

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Competing interests

None.

Ethical approval

Not required.

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CHAPTER 4

Factors associated with unfavorable treatment outcomes in new and previously treated TB patients in Uzbekistan: A five-year countrywide study

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Abstract

Background: TB is one of the main health priorities in Uzbekistan and relatively high rates of unfavorable treatment outcomes have recently been reported. This requires closer analysis to explain the reasons and recommend interventions to improve the situation. Thus, by using countrywide data this study sought to determine trends in unfavorable outcomes (lost-to-follow-ups, deaths and treatment failures) and describe their associations with socio-demographic and clinical factors.

Method: A countrywide retrospective cohort study of all new and previously treated TB patients registered in the National Tuberculosis programme between January 2006 and December 2010.

Results: Among 107,380 registered patients, 67% were adults, with smaller proportions of children (10%), adolescents (4%) and elderly patients (19%). Sixty per cent were male, 66% lived in rural areas, 1% were HIV-infected and 1% had a history of imprisonment. Pulmonary TB (PTB) was present in 77%, of which 43% were smear-positive and 53% were smear-negative. Overall, 83% of patients were successfully treated, 6% died, 6% were lost-to-follow-up, 3% failed treatment and 2% transferred out. Factors associated with death included being above 55 years of age, HIV-positive, sputum smear positive, previously treated, jobless and living in certain provinces. Factors associated with lost-to-follow-up were being male, previously treated, jobless, living in an urban area, and living in certain provinces. Having smear-positive PTB, being an adolescent, being urban population, being HIV-negative, previously treated, jobless and residing in particular provinces were associated with treatment failure.

Conclusion: Overall, 83% treatment success rate was achieved. However, our study findings highlight the need to improve TB services for certain vulnerable groups and in specific areas of the country. They also emphasize the need to develop unified monitoring and evaluation tools for drug-susceptible and drug-resistant TB, and call for better TB surveillance and coordination between provinces and neighbouring countries

Introduction

Tuberculosis (TB) remains a public health challenge worldwide and particularly in Central Asian countries. TB is one of the main health priorities in Uzbekistan and since 2004 the DOTS (directly observed treatment, short course) strategy has been progressively rolled out in the country. A recent study conducted in Tashkent, the capital city of Uzbekistan, showed that, of 1087 pulmonary TB patients started on treatment in 2005, 228 (21%) were lost to follow up [1]. Treatment failure among TB patients in certain provinces in Uzbekistan has also been relatively high (over 5-8%), and the prevalence of multidrug resistant TB (MDR-TB) among new cases has tended to increase over the years (Drug resistance survey - 14.2% in 2005 and 23.2% in 2011), [2, 3, 4].

Given the high rate of unfavorable treatment outcomes reported in some provinces, there is a need to analyze unfavorable outcomes countrywide and identify possible trends and associated risk factors that could guide the National TB programme (NTP) in further improvements. The NTP uses an individual-patient electronic database and this therefore allows for detailed analysis beyond the conventional monitoring and evaluation reports that are reliant on aggregate data. All TB patients registered in electronic database were on first-line treatment regimen. Of the drugs, isoniazid (H), rifampin (R), ethambutol (E), and pyrazinamide (Z) are considered first-line anti-TB drugs and form the core of standard treatment regimens for drug susceptible TB patients

Using countrywide TB data from Uzbekistan on TB patients receiving first-line treatment, the aim of our research was to determine a) trends in lost to follow-up, deaths and treatment failures between 2006 and 2010 and b) the socio-demographic and clinical risk factors associated with each of these unfavorable treatment outcomes.

Methods

Ethics

The study was approved by the "National Ethics Committee and Review Board" under the Ministry of Health (MoH) of Republic of Uzbekistan. The study satisfied the criteria for reports using routinely collected programmatic data set by the Médecins Sans Frontières Ethics Review Board (ERB), Geneva, Switzerland. Patient identifying information was removed prior to analysis. As this was a study of routinely collected monitoring data, patient consent was not required.

Study design

This was a retrospective cohort study of routinely collected NTP data for all TB patients registered and commenced on first-line treatment between January 2006 and December 2010. All patients were followed up until the end of treatment (6-8 months) to ascertain treatment outcomes.

Study setting

Previously part of the former Soviet Union, Uzbekistan is a country in Central Asia with an estimated population of more than 30 million. The country is divided into twelve provinces, the Republic of Karakalpakstan and the metropolitan area of Tashkent, the capital city.

The National TB Program (NTP)

TB control activities are coordinated countrywide by the Republican Specialized Scientific Practical Medical Center of Phthisiology and Pulmonology (RSSPMCPP), which is essentially the NTP. TB diagnosis and treatment are provided free of charge within the NTP – there are no private TB services. Nonetheless, first and second line anti-TB drugs are available on the open market as a result of there being no governmental regulations to forbid the selling of these drugs. All registered TB patients receive treatment in accordance with the Stop TB Strategy. The latest WHO Global TB Report [5] reports that only 35-50% of the national cases in Uzbekistan were detected between 2005 and 2010, implying that there may be a large number of TB cases left untreated or receiving 'unregistered' inefficacious treatments regimens in the country.

TB diagnosis and treatment

An established TB laboratory network in the country includes two National Reference Laboratories (NRL), five bacteriological laboratories and more than 300 smear microscopy laboratories, the latter of which perform direct microscopy of sputum collected in primary healthcare facilities. The mainstay of TB diagnosis in most provinces in Uzbekistan was through sputum smear microscopy or X-ray investigations. In accord with national guidelines [6], TB type was categorized as either pulmonary TB (PTB) or extrapulmonary TB (EPTB). PTB was defined as TB lesions involving the lung parenchyma, while TB lesions of the intra-thoracic lymph nodes (mediastinal and /or hilar), or tuberculosis pleurisies in the absence of radiographic changes in the lungs, were considered to be EPTB. If a patient presented with PTB and EPTB, they were recorded as having PTB when the pulmonary TB lesions were prominent; if however the patient had severe EPTB lesions (e.g. tuberculous meningitis) with limited forms of PTB lesions (smear-negative PTB), the patient was recorded as having EPTB.

Drug susceptibility testing (DST) during the study period could only be performed in two laboratories in Tashkent and Nukus. DST was performed using solid and liquid culture media and line probe assay (LPA) tests to determine type of drug resistance. Quality control in the two laboratories was ensured through routine checks by the Supra National Reference Laboratories (SNRL) in Borstel and Gauting, Germany. During the study period MDR-TB treatment was only available in Tashkent city, Nukus and the penitentiary system, and on account of limited bed capacity and resources, access to such treatment was not available for people residing in other provinces.

At the provincial level, TB treatment is provided under the supervision of the MoH and NTP at TB hospitals; at the district level, TB treatment is overseen by the TB dispensaries (outpatient care during the intensive phase and/or continuation phase of treatment) and also at the primary health care level (continuation phase of treatment) for both drug susceptible and MDR-TB patients in pilot areas. The Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund) provides all first-line anti-TB drugs and, since 2013, has provided all second-line drugs countrywide for treatment of drug resistant tuberculosis (DR-TB). A recent Drug Resistance Survey (DRS) showed high rates of MDR-TB among new and previously treated patients, 23% and 62% respectively (3). In response to the high levels of MDR-TB, the NTP developed the "Updated National Plan on prevention and control of M/XDR-TB for 2012-2015 in Uzbekistan" [7] which is in line with the "The Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-Resistant Tuberculosis in the WHO European Region, 2011-2015". This plan aims to decrease by 20 percentage points the proportion of MDR-TB among previously treated patients by the end of 2015; to diagnose at least 85% of all estimated MDR-TB patients by the end of 2015; to treat successfully at least 75% of all patients notified as having MDR-TB by the end of 2015. [8]

NTP monitoring system

Since 2005, an Epi-Info based-TB-ESCM (Tuberculosis Electronic Surveillance and Case Management) system has been implemented countrywide for disease surveillance and case management. All diagnosed patients are individually recorded in this electronic register with a unique registration number, and all of their clinical data are captured here.

TB treatment outcomes are in accord with WHO recommendations and described in national guidelines [6].

Study population

The study population included all TB patients on first line treatment (new and retreatment cases) registered countrywide in the NTP between January 2006 and December 2010.

Data collection and analysis

All data pertaining to this study were sourced from the TB ESCM electronic register. Patient characteristics were reported using summary statistics. Age categories were defined as follows: less than 15 years – child; 15-18 years – adolescent, 19-55 years – adult; 56 years or above – elderly. Unfavorable treatment outcomes were defined as death, treatment failure and lost to follow up, and each of these outcomes was assessed separately. Risk factors for unfavorable TB treatment outcomes were determined by crude odds ratios (ORs) and adjusted ORs, comparing the odds of having that outcome of interest with the odds of not having that outcome of interest (i.e. having any other outcome). Adjusted

ORs were determined through multivariate logistic regression using a backward stepwise elimination approach until all remaining variables in the model were significant at P=0.05 or less. All related P-values were based on the Walds test and 95% confidence intervals were used throughout. Due to the incomplete ascertainment of transfer outs (many of which were considered to be failures secondary to MDR-TB), a sensitivity analysis was run in which all transfer outs were assumed to be failures.

The study was carried out between June 2013 and June 2014 using EpiData Analysis software (version 2.2.2.182, EpiData Association, Odense, Denmark) and STATA/IC 11 software (Stata corporation, College Station, Texas 77845, USA).

Results

Characteristics of the study population: Between 2006 and 2010, 110,146 TB patients on first-line drug regimen were registered in Uzbekistan. Of these, one percent (1,226) had treatment outcome missing and 1.4% (1540) did not have a confirmed TB diagnosis; as such these patients were excluded from the analysis. Table 1 shows the baseline demographic and clinical characteristics of the 107,380 patients included in the study. Adults (19-55 years) made up 67% (71,522) of the patients, while 10% (11,519) were children (<15 years) and 4% (4764) were adolescents (15-18 years). Almost 60% were male and 66% from rural areas (70,705). New patients made up 75% (81,016) of the caseload, while 25% (26364) were previously treated patients. One percent (984) of patients was human immunodeficiency virus (HIV) positive and less than one percent (586) had a history of imprisonment. Seventy seven percent (82,686) of patients had pulmonary tuberculosis (PTB), of which 43% (35,178) were sputum smear positive, 53% (44,205) sputum smear negative and 3,303 with no or unknown sputum results.

Table 1. Socio-demographic and clinical characteristics and treatment outcomes of tuberculosis patients, Uzbekistan 2006- 2010

Variables	**n (%)**
Total	**107380**
Age (years)	
Children (<15)	11519 (11)
Adolescent (15-18)	4764 (4)
Adults (19-55)	71522 (67)
Elderly patients (>55)	19575 (18)
Sex	
Male	63724 (59)
Female	43656 (41)
Place of residence	
Urban	32752 (30)
Rural	70705 (66)
Unknown	3923 (4)
Provinces	

Republic of Karakalpakstan	13905 (13)
Tashkent city	8504 (8)
Andijan province	8525 (8)
Bukhara province	4857 (4)
Jizzakh province	4873 (5)
Kashkadarya province	8593 (8)
Navoi province	4258 (4)
Namangan province	8062 (8)
Samarkand province	11202 (10)
Surkhandarya province	5455 (5)
Syrdarya province	2601 (3)
Tashkent province	11314 (11)
Fergana province	9830 (9)
Khorezm province	5164 (5)
Navoi mining company	229 (<1)
Unknown	8 (<1)
HIV status	
HIV positive	984 (1)
HIV negative	96524 (90)
Unknown	9872 (9)
TB type	
PTB	
Smear positive	35178 (33)
Smear negative	44205 (41)
No sputum/no sputum result	3303 (3)
EPTB	24694 (23)
History of TB treatment	
New cases	81016 (75)
Retreatment cases	26364 (25)
Treatment category	
0	93 (<1)
I	76548 (71)
II	25986 (24)
III	4752 (4)
Unknown	1 (<1)
History of contact with TB patient	
No	90673 (85)
Yes	5590 (5)
Unknown	11117 (10)
History of imprisonment	
No	44147 (41)
Yes	586 (<1)
Unknown	62647 (58)
Occupational status	
Worker	12105 (11)
Jobless	48569 (45)
Pre-school age	2994 (3)
Pupil/student	11186 (10)
Pensioner	13898 (13)
Handicapped	5996 (6)
Unknown	12632 (12)
Treatment outcomes	
Cured	25404 (23)

Treatment completed	64218 (60)
Died	5953 (6)
Loss to follow up	6768 (6)
Failure	3312 (3)
Transferred out	1725 (2)

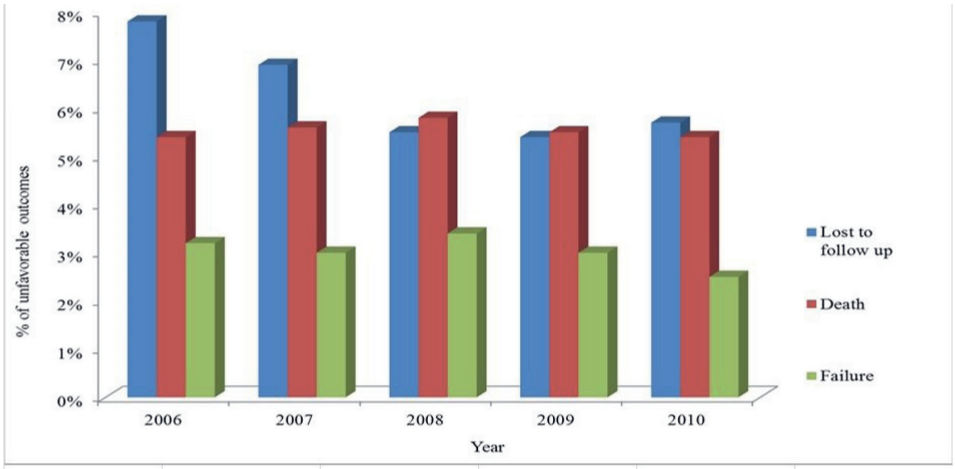
TB, Tuberculosis; PTB, Pulmonary TB; EPTB, Extrapulmonary TB;

Treatment outcomes and their trends

Overall, 83% (89,622) of patients were successfully treated (cured or treatment completed), 6% (5,953) died, 6% (6,768) were lost to follow up, 3% (3,312) failed treatment and 2% (1,725) were transferred out. Trends in the different unfavorable outcomes between 2006 and 2010 are shown in Fig. 1**.** Deaths and treatment failures have remained stable over time, while lost to follow up decreased from 7.8% in 2006 to 5.7% in 2010. Table 2 shows a breakdown of treatment outcomes by TB type and TB retreatment history**.** Of note, new smear positive cases had a treatment success rate of 82%, new EPTB cases had a treatment success rate of 93%, and retreatment cases had a treatment success rate of 73%.

Table 2. Treatment outcomes of all registered tuberculosis patients by TB type and treatment history, Uzbekistan 2006-2010

	n	**Treatment success n (%)**	**Died n (%)**	**Treatment Failure n (%)**	**Lost to follow up n (%)**	**Transferred out n (%)**
New cases						
Smear positive	24480	19971 (82)	1437 (6)	1322 (5)	1257 (5)	493 (2)
Smear negative	32240	28198 (87)	1513 (5)	405 (1)	1750 (5)	374 (1)
No sputum/no result	1940	1572 (81)	129 (7)	100 (5)	101 (5)	38 (1)
Extrapulmonary	22356	20704 (93)	414 (2)	31 (0.1)	1054 (5)	153 (0.7)
Retreatment cases	26364	19177 (73)	2460 (9)	1454 (6)	2606 (10)	667 (3)
Total	107380	89622 (83)	5953 (6)	3312 (3)	6768 (6)	1725 (6)



Year	2006	2007	2008	2009	2010
Total registered cases	23534	22050	20990	20937	19869
Lost to follow up, n (%)	1833 (8)	1515 (7)	1158 (6)	1124 (5)	1138 (6)
Died, n (%)	1271 (5)	1230 (6)	1221 (6)	1151 (6)	1080 (5)
Treatment failure, n (%)	746 (3)	660 (3)	712 (3)	623 (3)	571 (3)

Figure 1. Unfavorable treatment outcomes over five years in Uzbekistan 2006-2010

Factors associated with deaths, lost to follow-ups and treatment failures

Based on a multivariate analysis, factors found to be associated with death included being elderly (>55), being male, living in an urban area, having smear positive PTB, having a history of TB treatment, being HIV positive and being jobless, a pensioner or handicapped. The three provinces with the highest mortality were Samarkand province, Surkhandarya province and Tashkent city (Table 3)**.** Being a child or adolescent, and having EPTB, was protective for dying.

Table 3. Factors associated with deaths among TB patients in Uzbekistan 2006-2010

Variable	n	Deaths n (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	*P*-value
Total	107380	5953 (6)	-	-	-
Age (years)					
Children (<15)	11519	75 (1)	0.1 (0.09-0.1)	0.3 (0.2-0.5)	<0.001
Adolescent (15-18)	4764	96 (2)	0.4 (0.3-0.5)	0.7 (0.5-0.9)	0.005
Adults (19-55)	71522	3759 (5)	1	1	
Elderly patients (>55)	19575	2023 (10)	2.1 (2.0-2.2	1.9 (1.6-2.1)	<0.001
Sex					
Male	63724	3855 (6)	1.3 (1.2-1.3)	1.3 (1.2-1.4)	0.001
Female	43656	2098 (5)	1	1	
Place of residence					
Urban	32752	2257 (7)	1.5 (1.4-1.6)	1. 3 (1.2-1.4)	<0.001
Rural	70705	3343 (5)	1	1	
Unknown	3923	353 (9)	2.0 (1.8-2.2)		
Province					
Rep. of Karakalpakstan	13905	702 (5)	1.7 (1.4-2.0)	1.1 (0.9-1.4)	0.40
Tashkent city	8504	849 (10)	3.5 (2.9-4.2)	1.9 (1.5-2.4)	0.001
Andijan province	8525	399 (5)	1.5 (1.3-1.9)	1.3 (1.0-1.6)	0.07
Bukhara province	4857	220 (4)	1.5 (1.2-1.9)	1.1 (0.9-1.5)	0.31
Jizzakh province	4873	147 (3)	1.0 (0.8-1.2)	0.9 (0.7-1.3)	0.69
Kashkadarya province	8593	279 (3)	1.1 (0.9-1.3)	1.2 (0.9-1.5)	0.17
Navoi province	4258	131 (3)	1	1	
Namangan province	8062	361 (4)	1.4 (1.2-1.8)	1.4 (1.1-1.8)	0.004
Samarkand province	11202	998 (9)	3.1 (2.6-3.7)	2.3 (1.8-2.9)	0.001
Surkhandarya province	5455	295 (5)	1.8 (1.5-2.2)	1.8 (1.4-2.3)	0.001
Syrdarya province	2601	144 (6)	1.8 (1.4-2.4)	1.7 (1.3-2.3)	0.001
Tashkent province	11314	622 (6)	1.8 (1.5-2.2)	1.6 (1.2-2.0)	0.001
Fergana province	9830	568 (6)	1.9 (1.6-2.3)	1.5 (1.2-1.9)	0.001

Khorezm province	5164	228 (4)	1.5 (1.2-1.8)	1.2 (0.9-1.5)	0.21
Navoi mining company	229	9 (4)	1.3 (0.6-2.6)	1.3 (0.6-2.7)	0.50
Unknown	8	1 (12)			
HIV status					
HIV positive	984	280 (29)	7.5 (6.5-8.7)	8.1 (6.9-9.5)	<0.001
HIV negative	96524	4852 (5)	1	1	
Unknown status	9872	821 (8.3)	1.7 (1.6-1.9)		
TB type					
PTB					
Smear positive	35178	2875 (8)	1.6 (1.5-1.7)	1.5 (1.5-1.7)	<0.001
Smear negative	44205	2277 (5)	1	1	
No sputum/no result	3303	293 (9)	1.8 (1.6-2.0)	1.6 (1.3-1.8)	<0.001
EPTB	24694	508 (2)	0.4 (0.4-0.4)	0.7 (0.6-0.8)	<0.001
History of TB treatment					
New cases	81016	3493 (4)	1	1	
Retreatment cases	26364	2460 (9)	2.3 (2.2-2.4)	1.7 (1.5-1.8)	<0.001
Treatment category					
0[b]	93	13 (14)	3.4 (1.9-6.2)		
I	76548	3454 (5)	1		
II	25986	2444 (10)	2.2 (2.1-2.3)		
III	4752	42 (1)	0.2 (0.1-0.3)		
Unknown	1	0 (0)			
History of contact with TB patient					
No	90673	4892 (5)	1.5 (1.3-1.7)		
Yes	5590	206 (4)	1		
Unknown	11117	855 (8)			
History of imprisonment[c]					
No	44147	1893 (4)	1		
Yes	586	39 (7)	1.6 (1.1-2.2)		

Unknown	62647	4021 (6)	1.5 (1.4-1.6)		
Occupational status					
Worker	12105	381 (3)	1	1	
Jobless	48569	2476 (5)	1.7 (1.5-1.8)	1.5 (1.4-1.7)	<0.001
Pre-school age	2994	28 (1)	0.3 (0.2-0.4)	1.0 (0.5-1.9)	0.96
Pupil/student	11186	82 (1)	0.2 (0.2-0.3)	0.8 (0.6-1.1)	0.21
Pensioner	13898	1461 (11)	3.6 (3.2-4.1)	2.1 (1.8-2.5)	<0.001
Handicapped Unknown	5996 12632	585 (10) 940 (7)	3.3 (2.9-3.8) 2.5 (2.2-2.8)	2.4 (2.1-2.7)	<0.001

TB, Tuberculosis; PTB, Pulmonary TB; EPTB, Extrapulmonary TB; OR, Odds Ratio, CI, Confidence Interval

[a] Adjusted odds ratios only presented for variables included in the multivariate model; 92,812 records included in the multivariate model

[b] 0- patients who refused treatment, or treatment category not defined, or where TB diagnosis was based on the findings of a post-mortem

[c] Data should not be considered relevant as unknown cases more than 50% in this group of patients.

Factors associated with lost to follow-up were being male, living in an urban area, being HIV positive, having previous TB treatment history, being jobless, and living in the following provinces: Bukhara province, Tashkent province, Andijan province, (Table 4). Being an adolescent was protective for being lost to follow-up.

Table 4. Factors associated with loss to follow-up among TB patients in Uzbekistan 2006-2010

Variable	**N**	**Loss to follow up n (%)**	**Crude OR (95% CI)**	**Adjusted OR[a] (95% CI)**	***P*-value**
Total	107380	6768 (6)	-	-	-
Age (years)					
Children (<15)	11519	455 (4)	0.5 (0.5-0.6)	0.8 (0.6-1.0)	0.06
Adolescent (15-18)	4764	190 (4)	0.5 (0.5-0.6)	0.7 (0.6-0.8)	<0.001
Adults (19-55)	71522	5083 (7)	1	1	
Elderly patients (>55)	19575	1040 (5)	0.7 (0.7-0.8)	0.9 (0.8-1.0)	0.11
Sex					
Male	63724	4645 (7)	1.5 (1.5-1.6)	1.4 (1.4-1.5)	<0.001
Female	43656	2123 (5)	1	1	
Place of residence					
Urban	32752	2800 (9)	1.8 (1.7-1.9)	1.8 (1.7-2.0)	<0.001
Rural	70705	3560 (5)	1	1	
Unknown	3923	408 (10)	2.2 (2.0-2.4)		
Province					
Republic of Karakalpakstan	13905	693 (5)	1.4 (1.2-1.7)	0.9 (0.7-1.2)	0.54
Tashkent city	8504	528 (6)	1.8 (1.5-2.1)	0.8 (0.6-1.0)	0.03
Andijan province	8525	722 (8)	2.5 (2.1-2.9)	2.1 (1.6-2.6)	<0.001
Bukhara province	4857	564 (12)	3.5 (2.9-4.2)	3.3 (2.6-4.1)	<0.001
Jizzakh province	4873	177 (4)	1.0 (0.8-1.3)	1.0 (0.7-1.3)	0.83
Kashkadarya province	8593	239 (3)	0.8 (0.6-0.9)	0.7 (0.6-0.9)	0.02
Navoi province	4258	154 (4)	1	1	
Namangan province	8062	467 (6)	1.6 (1.4-2.0)	1.4 (1.1-1.7)	0.01
Samarkand province	11202	585 (5)	1.5 (1.2-1.8)	1.1 (1.1-1.7)	0.008
Surkhandarya province	5455	377 (7)	2.0 (1.6-2.4)	1.8 (1.4-2.3)	<0.001
Syrdarya province	2601	116 (5)	1.2 (1.0-1.6)	1.0 (0.8-1.4)	0.93
Tashkent province	11314	1195 (11)	3.1 (2.7-3.7)	2.4 (1.9-3.0)	<0.001
Fergana province	9830	636 (7)	1.8 (1.5-2.2)	1.6 (1.3-2.0)	<0.001
Khorezm province	5164	300 (6)	1.6 (1.3-2.0)	1.4 (1.1-1.8)	0.01
Navoi mining company	229	11 (5)	1.3 (0.7-2.5)	1.1 (0.5-2.1)	0.85
Unknown	8	2 (25)	8.9 (1.8-44.4)		
HIV status					
HIV positive	984	81 (8)	1.5 (1.2-1.8)		
HIV negative	96524	5607 (6)	1		
Unknown	9872	1080 (11)	2.0 (1.9-2.1)		
TB type					
PTB					

Smear positive	35178	2416 (7)	1.1 (1.0-1.1)		
Smear negative	44205	2893 (7)	1		
No sputum/no result	3303	277 (7)	1.1 (0.9-1.2)		
EPTB	24694	1232 (5)	0.7 (0.7-0.8)		
History of TB treatment					
New cases	81016	4162 (5)	1	1	
Retreatment cases	26364	2606 (10)	2.0 (1.9-2.1)	1.8 (1.7-1.9)	<0.001
TB treatment category					
0[b]	93	7 (8)	1.5 (0.7-3.3)		
I	76548	3911 (5)	1		
II	25986	2580 (10)	2.0 (1.9-2.2)		
III	4752	270 (6)	1.1 (1.0-1.3)		
Unknown	1	0 (0)	-		
History of contact with TB patient					
No	90673	309 (6)	1.4 (1.3-1.5)		
Yes	5590	5415 (6)	1		
Unknown	11117	1044 (9)			
History of imprisonment[c]					
No	44147	2614 (6)	1		
Yes	586	62 (11)	1.9 (1.4-2.5)		
Unknown	62647	4092 (7)	1.1 (1.1-1.2)		
Occupational status					
Worker	12105	531 (4)	1	1	
Jobless	48569	3492 (7)	1.7 (1.5-1.9)	1.7 (1.6-1.9)	<0.001
Pre-school age	2994	140 (5)	1.1 (0.9-1.3)	1.5 (1.1-2.0)	0.02
Pupil/student	11186	399 (4)	0.8 (0.7-0.9)	1.2 (0.9-1.5)	0.25
Pensioner	13898	674 (5)	1.1 (1.0-1.2)	1.3 (1.1-1.6)	0.002
Handicapped	5996	423 (7)	1.7 (1.5-1.9)	1.3 (1.1-1.5)	0.001
Unknown	12632	1109 (9)	2.1 (1.9-2.3)		

TB, Tuberculosis; PTB, Pulmonary TB; EPTB, Extrapulmonary TB; OR, Odds Ratio, CI, Confidence Interval

[a]Adjusted odds ratios only presented for variables included in the multivariate model; 92812 records included in the multivariate model

[b]0- patients who refused treatment, or treatment category not defined, or where TB diagnosis was based on the findings of a post-mortem

[c]Data should not be considered relevant as unknown cases more than 50% in this group of patients

Factors associated with treatment failure included being adolescent, urban area population, having positive sputum result, previous treatment history, being HIV negative, being jobless, and residing in the following provinces: Fergana province, Tashkent city,

Republic of Karakalpakstan, (Table 5). Being a child and having EPTB, was protective for failing treatment.

Table 5. Factors associated with treatment failure in TB patients in Uzbekistan, 2006-2010

Variables	n (%)	Treatment failure n (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	*P*-value
Total	107380	3312 (3)			
Age (years)					
Children (<15)	11519	32 (<1)	0.07 (0.05-0.1)	0.6 (0.3-0.9)	0.02
Adolescent (15-18)	4764	170 (4)	0.9 (0.8-1.1)	1.3 (1.1-1.7)	0.01
Adults (19-55)	71522	2716 (4)	1	1	
Elderly patients (>55)	19575	394 (2)	0.5 (0.5-0.6)	0.8 (0.7-1.0)	0.07
Sex					
Male	63724	2070 (3)	1.2 (1.1-1.2)		
Female	43656	1242 (3)	1		
Place of residence					
Urban	32752	1462 (5)	2.0 (1.9-2.2)	1.5 (1.4-1.7)	<0.001
Rural	70705	1590 (2)	1	1	
Unknown	3923	260 (7)	3.2 (2.7-3.5)		
Province					
Rep of Karakalpakstan	13905	682 (5)	3.6 (2.7-4.5)	2.6 (1.9-3.7)	<0.001
Tashkent city	8504	427 (5)	3.6 (2.7-4.7)	2.1 (1.4-2.9)	0.001
Andijan province	8525	304 (4)	2.5 (1.9-3.3)	1.9 (1.4-2.8)	<0.001
Bukhara province	4857	78 (2)	1.1 (0.8-1.5)	1.2 (0.8-1.8)	0.42
Jizzakh province	4873	61 (1)	0.9 (0.6-1.2)	0.6 (0.4-0.9)	0.02
Kashkadarya province	8593	17 (<1)	0.1 (0.1-0.2)	0.1 (0.1-0.2)	<0.001
Navoi province	4258	62 (2)	1	1	
Namangan province	8062	181 (2)	1.6 (1.2-2.1)	1.4 (1.0-2.0)	0.09
Samarkand province	11202	239 (2)	1.5 (1.1-2.0)	1.4 (1.0-1.9)	0.09
Surkhandarya province	5455	79 (2)	1.0 (0.7-1.4)	0.8 (0.5-1.1)	0.20
Syrdarya province	2601	85 (3)	2.3 (1.6-3.2)	1.7 (1.1-2.5)	0.01
Tashkent province	11314	492 (4)	3.1 (2.4-4.0)	2.1 (1.5-3.0)	<0.001
Fergana province	9830	447 (5)	3.2 (2.5-4.2)	2.8 (2.0-3.9)	<0.001
Khorezm province	5164	151 (3)	2 (1.5-2.7)	1.2 (0.8-1.8)	0.27
Navoi mining	229	6 (3)	1.8 (0.8-4.3)	2.7 (1.1-6.5)	0.03
Unknown	8	0 (0)	-	-	
HIV status					
Positive	984	23 (2)	1	1	
Negative	96524	2656 (3)	1.2 (0.8-1.8)	1.6 (1.1-2.5)	0.02
Unknown	9872	635 (7)	2.9 (1.9-4.4)		
TB type					
PTB					
Smear positive	35178	2482 (7)	5.5 (5.0-6.0)	5.5 (4.9-6.0)	<0.001

Smear negative	44205	606 (1)	1	1	
No sputum/no result	3303	192 (6)	4.4 (3.8-5.2)	4.3 (3.5-5.3)	<0.001
EPTB	24694	32 (0.1)	0.09 (0.07-0.1)	0.2 (0.1-0.2)	<0.001
History of TB treatment					
New cases	81016	1858 (2)	1	1	
Retreatment cases	26364	1454 (6)	2.5 (2.3-2.7)	1.7 (1.5-1.8)	<0.001
Treatment category					
0[b]	93	1 (1)	0.4 (0.06-3.1)		
I	76548	1856 (2)	1		
II	25986	1447 (6)	0.07 (0.03-0.1)		
III	4752	8 (0.2)	-		
Unknown	1	1 (0)			
TB contact					
No	90673	2425 (3)	1.6 (1.4-1.8)	1.6 (1.4-1.8)	<0.001
Yes	5590	887 (6)	1	1	
Unknown	11117	0 (0)			
History of imprisonment[c]					
No	44147	1037 (2)	1		
Yes	586	19 (3)	1.4 (0.9-2.2)		
Unknown	62647	2256 (4)	1.6 (1.4-1.7)		
Occupational status					
Worker	12105	345 (3)	1	1	
Jobless	48569	1712 (4)	1.3 (1.1-1.4)	1.1 (1.0-1.3)	0.03
Pre-school age	2994	1 (0.03)	0.01 (0.002-0.8)	0.1 (0.01-0.8)	0.03
Pupil/student	11186	103 (0.9)	0.3 (0.3-0.4)	0.9 (0.6-1.2)	0.37
Pensioner	13898	225 (2)	0.6 (0.5-0.7)	0.7 (0.5-0.9)	0.005
Handicapped	5996	247 (4)	1.5 (1.2-1.7)	1.1 (0.9-1.3)	0.22
Unknown	12632	679 (6)	2 (1.7-2.3)	-	-

TB, Tuberculosis; PTB, Pulmonary TB; EPTB, Extrapulmonary TB; OR, Odds Ratio, CI, Confidence Interval

[a]Adjusted odds ratios only presented for variables included in the multivariate model; 92055 records included in the multivariate model

[b]0- patients who refused treatment, or treatment category not defined, or where TB diagnosis was based on findings of a post-mortem

[c]Data should not be considered relevant as unknown cases more than 50% in this group of patients

Discussion

This is the first report from Uzbekistan, and one of the first from a former Soviet Union Country, describing the association of risk factors with treatment outcomes of the patients under first-line drug regimen over the course of five years. Systematic reviews have highlighted that there are limited large-scale data on TB treatment outcomes. Another

systematic review of national-level TB treatment outcomes among the 30 European Union /European Economic Area countries indicated the same [9]. The WHO Global TB Report provide such data at national level; however detailed analysis of individual patient data, as well as associations between unfavorable treatment outcomes and selected demographic and clinical characteristics, are not reported [5].

Our study has shown promising treatment success (83%) among registered TB patients on first line treatment in Uzbekistan, with these data closely corroborating the data on treatment outcomes reported by WHO for Uzbekistan [5]. The overall treatment success rate that we report is marginally higher that reported by WHO because WHO only considers new smear positive cases in its analysis, whereas we have reported on all registered patients. This includes new smear negative and EPTB cases who have higher rates of treatment success than new smear positive cases. Moreover, we have been able to describe in detail patient characteristics together with certain factors that are associated with unfavorable treatment outcomes. These findings may help the national programme to define strategies and targeted interventions for the most vulnerable populations in order to further improve TB control.

Trends in unfavorable TB outcomes remained relatively stable over the five-year period. Interestingly however, despite stable treatment failure rates, a recent DRS survey revealed alarmingly high rates of DR TB among new and previously treated cases [3]. Various factors may underpin this situation, including low case detection rate. Recent estimates presented in the latest WHO Global TB Report [5] suggest that only 50% of TB cases in Uzbekistan are being detected and put on 'registered' treatment. This indicates that a large number of TB cases are either going untreated or, due to factors such as stigma, are seeking treatment from 'unofficial' sources, the latter of which may be associated with patients receiving inefficacious treatment regimens. We can only speculate, but 'unregistered' cases may be a prime driver of the MDR-TB epidemic and this calls for urgent measures to improve case detection in Uzbekistan. In the context of Uzbekistan, this could be addressed by a) strengthening the capacity of primary health care facilities in TB case detection, given that these facilities are usually the first point of contact for most patients; b) improving the performance of microscopy laboratories located in rural places; c) raising community awareness on TB. During the study period, access to MDR-TB diagnosis and treatment was only guaranteed for patients residing in Tashkent city, Nukus city and in penitentiary system. It is encouraging to see that since 2013, MDR-TB treatment has become available for everyone in the country and, since 2014, Xpert MTB/RIF has become available in all provinces.

In our analysis we went beyond the usual convention of just stratifying patients according to whether they were adults or children, and also considered adolescents (15-18 years)

and elderly patients (>55 years) – two groups that are rarely examined despite there being evidence that these are particularly vulnerable sub-groups in the context of other diseases [10]. In our study, adolescents had a higher likelihood of treatment failure and elderly patients had higher mortality. The latter has been reported in other settings [11,12,13] and may be due to age-related factors such as co-existing morbidities, like diabetes mellitus (which has been shown to increase the case fatality rate during TB treatment) [14], immunosuppression and a greater likelihood of unfavorable drug reactions [15,16].

The degree of unfavorable treatment outcomes between provinces varied quite notably, with higher mortality, lost to follow-up and treatment failure observed in the capital city Tashkent, Fergana, and in the Republic of Karakalpakstan which is also known to have the highest rate of drug-resistant TB in the world [3, 17, 18]. The differences between provinces may be explained by a number of factors such as i) variations in drug resistance prevalence and resistance patterns (for example, the highest rates of MDR-TB have been reported in the Republic of Karakalpakstan [3] which in turn, is the province with the highest treatment failure; in contrast, the lowest rates of MDR-TB are reported in Surkhandarya province which concordantly has a relatively low odds of treatment failure compared with other provinces, ii) the performance of the local programme in terms of directly observed treatment (DOT) management, (i.e. poor supervision at the primary health facilities of patients' anti-TB drug intake during the continuation phase of treatment), iii) the performance of the local primary health care services in relation to TB case detection of TB through microscopy, iv) the availability of first and second line anti TB drugs on the open market (which may be inappropriately used by doctors (private and public based) who are treating 'unregistered' TB patients (NB. This is forbidden by national regulations) [6], and/or v) patient characteristics such as migration and population mobility. Operational research at the level of the province may help to identify these specific factors. Qualitative research methods in particular (such as direct observation, in-depth interviews with local key stake holders, and "content analysis" of local reports and archives), may provide additional information that quantitative data currently do not reveal. We have hypothesized several factors; of these, differences in performance between provinces, availability of TB-drugs on the "open market", and migration and mobility patterns, could be explored with qualitative or mixed methods.

There were disparities across all unfavorable outcomes when comparing urban and rural areas. This finding has not been reported in other similar settings and thus we can only speculate on possible reasons for it. Deaths, lost to follow-ups, and treatment failures were all more common among urban than rural patients. Possible reasons for this may be related to differences in patients and/or differences in TB control activities between urban and rural areas. Co-morbidities such as diabetes mellitus may be more prevalent in urban rather than rural communities [19], the latter of which is known to be associated with a

higher likelihood of unfavorable TB outcomes [20]. Identifying what these specific reasons are would require further investigation.

As shown in previous studies [21, 22, 23], treatment outcomes were worse among HIV-positive TB patients compared to HIV negative TB patients, especially death. In contrast, HIV-positive TB patients had lower lost to follow-up and treatment failure. This could be partially accounted for by the higher mortality among HIV positive TB patients – i.e. these patients are more likely to die before it becomes evident that they have been lost to follow-up or failed treatment [24]; it may also reflect better adherence to treatment among these patients. It is important to note that HIV-testing uptake was high in this national TB cohort and the country should maintain and further improve this, even though Uzbekistan is a low prevalence country.

Our study shows that treatment outcomes are poor among pulmonary sputum positive cases, and among previously treated patients rather than patients with negative sputum results and new TB cases. Our findings reflect what many other studies have shown [25, 26].

The main strength of the study relates to the large countrywide size and national representativeness of the data. It is one of the first studies to have used countrywide TB data to assess risk factors associated with unfavorable treatment outcomes, and to have analyzed individual patient data rather than aggregate data. Most national TB programmes report only aggregate data as maintaining electronic databases that collect individual patient data is too resource demanding.

There are several study limitations. First, the study was reliant on routinely collected data which may have been subject to reporting errors typically encountered in programmatic settings (such as incomplete data, inaccurate data, typing errors etc.). Second, we were not able to analyze some particularly interesting subgroups of patients such as inmates, as large amounts of these data were incomplete. Finally, a major limitation was the misclassification of 'transfer-outs'. Between 2003 and 2005, two MDR-TB pilot programmes were started in Karakalpakstan and the capital city Tashkent. Patients diagnosed with MDR-TB were transferred to the pilot clinics and their records were transferred to the MDR-TB register. In many instances, these patients were classified in the national database as "transferred out" rather than "treatment failure". Furthermore, for patients who were transferred out to a different district/province, the national database should have been updated to reflect the final outcome for that patient. This however never happened. Therefore, in this study the outcome "transferred out" consisted of patients for whom the final outcome was not ascertained and patients who were transferred into the MDR TB register after failing standard treatment. As such, a proportion of the transfer outs were

essentially treatment failures, although this proportion remains unknown. To take account of this discrepancy we ran a sensitivity analysis in which all transfer outs were considered to be failures. When transfer-outs were combined with failures like this however, there were no notable differences in the factors associated with this combined outcome in comparison to those factors identified as being associated with treatment failure alone. This misclassification in standard treatment outcome reporting needs to be addressed going forwards.

In conclusion, this study has demonstrated how countrywide data can be used to monitor trends in TB outcomes and guide the NTP in identifying areas where targeted strategies need to be deployed for vulnerable groups and in certain parts of the country. We also highlight the need to unify the monitoring and reporting of TB outcomes between the national database for standard TB treatment and the database for MDR-TB. Finally, as migration between countries continues to increase surveillance of treatment failures and coordination of TB case management between neighboring countries needs to be reinforced.

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Conflict of interest

None declared.

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CHAPTER 5

5

Drug-resistant tuberculosis in Eastern Europe: challenges and ways forward

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Introduction

Encouragingly, global rates of new tuberculosis (TB) cases have been falling since 2005, in line with the Millennium Development Goal targets; however, cases of multidrug-resistant (MDR-) and extensively drug-resistant TB (XDR-TB) have been increasing. Fifteen of the world's 27 high MDR- and XDR-TB burden countries are in the World Health Organization (WHO) European Region, of which 10 are in Eastern Europe (including Baltic and Caucasus countries). To address the MDR- and XDR-TB situation in the WHO European Region, a Consolidated Action Plan to Prevent and Combat M/XDR-TB (2011–2015) was developed for all 53 Member States and implemented in 2011. Since the implementation of the Action Plan, the proportion of MDR-TB appears largely to have levelled off among bacteriologically confirmed TB cases in high-burden countries with universal or near universal (>95%) first-line drug susceptibility testing (DST). The treatment success rate, however, continues to decrease. A contributing factor is the substantial proportion of MDR-TB cases that are additionally resistant to either a fluoroquinolone, a second-line injectable agent or both (XDR-TB); high-burden country proportions range from 12.6% to 80.4%. Proportions of XDR-TB range from 5% to 24.8%. Despite much progress in Eastern Europe, critical challenges remain as regards access to appropriate treatment regimens; patient hospitalisation; scale-up of laboratory capacity, including the use of rapid diagnostics and second-line DST; vulnerable populations; human resources; and financing. Solutions to these challenges are aligned with the Post-2015 Global TB strategy. As a first step, the global strategy should be adapted at regional and country levels to serve as a framework for immediate actions as well as longer-term ways forward.

More than 50 years after the first anti-tuberculosis chemotherapeutic drugs were introduced, tuberculosis (TB) remains a leading cause of death and life-threatening illness, disproportionately affecting low- and middle-income countries. In 2012, there were approximately 8.6 million new cases of TB worldwide, and 1.3 million people died from the disease.1 In addition, treatment success rates have been severely compromised in recent years due to the increasing prevalence of multidrug-resistant (MDR-) and extensively drug-resistant TB (XDR-TB).[1,2] Although, encouragingly, global rates of new TB cases have been falling since 2005, in line with Millennium Development Goal (MDG) targets,[3] MDR- and XDR-TB cases have been increasing, with an estimated 450 000 new cases in 2012.[1] This review will focus on drug-resistant TB in the eastern European sub-region (including Baltic and Caucasus countries), which has one of the highest rates of MDR- and XDR-TB in the world; the challenges to MDR- and XDR-TB control; and potential ways forward.

Countries included in this review

The high MDR-TB burden countries in Eastern Europe (including Baltic and Caucasus countries) that have been included in this review and which are within the World Health Organization (WHO) European Region, are Armenia, Azerbaijan, Belarus, Estonia, Georgia,

Latvia, Lithuania, the Republic of Moldova, the Russian Federation and Ukraine.[1] We limited the scope of this review geographically to countries from this sub-region, as they were eligible to participate in the Structured Operational Research and Training Initiative (SORT IT) Eastern European Programme 2012–2014,[4] through which the research presented in this supplement of *Public Health Action* was conducted.

Background to the MDR- and XDR-TB situation in the WHO European Region

MDR-TB is caused by *Mycobacterium tuberculosis* that is resistant to at least isoniazid (INH) and rifampicin (RMP), the two most potent anti-tuberculosis drugs. XDR-TB is defined as MDR-TB plus any fluoroquinolone and at least one injectable second-line drug (i.e., amikacin, kanamycin or capreomycin). Drug-resistant TB can occur due either to transmission of already resistant strains of *M. tuberculosis*[5] or to suboptimal treatment of susceptible strains, which can develop resistance. [6] The duration of treatment is longer for MDR-TB (up to 2 years) than for drug-susceptible TB (6–9 months), with a significantly higher risk of adverse drug reactions[7,8] and unsuccessful treatment outcomes, particularly death.[9–12] These risks are even higher for XDR-TB.[13,14]

Fifteen of the world's 27 countries with a high MDR- and XDR-TB burden are in the WHO European Region (Figure 1).[15,16] With the dissolution of the Union of Soviet Socialist Republics in the early 1990s, TB and MDR-TB case rates began to increase in the newly independent states, largely due to the ensuing socio-economic crisis and deterioration of the health care system (Figure 2).[17,18] Currently, all high-burden MDR-TB countries in the WHO European Region are in the east, and 99% of the region's MDR-TB cases occur in these countries.[15,16]

In 2010, to address the MDR- and XDR-TB situation in the Region, a Consolidated Action Plan to Prevent and Combat M/XDR-TB (2011–2015) was developed for all 53 member states.[16] The goal of the plan is to contain the spread of drug-resistant TB by achieving universal access to prevention, diagnosis and treatment of MDR- and XDR-TB in all member states in the Region by 2015.[16] The plan, which has six strategic directions and seven areas of intervention, is aligned with the Global Plan to Stop TB 2011–2015,[19] with the following specific targets to be met by the end of 2015: reduce by 20% the proportion of MDR-TB among retreatment patients, diagnose at least 85% of all estimated MDR-TB patients, and successfully treat at least 75% of all patients notified as having MDR-TB. The plan is also designed to address causal determinants of and barriers to TB control, including the use of operational research to inform policy guidance and models of care to reach the targets set forth. Endorsement and implementation of the plan began in 2011.

The burden of MDR- and XDR-TB in the WHO European Region

Currently, while only approximately 4% of the global burden of TB is found in the WHO European Region, atotal of 25% of the world's burden of MDR-TB is also found here,

indicating the crucial importance of MDR-TB for this region.[1] The current estimated annual incidence and proportion of MDR-TB among new and previously treated TB cases in the high-burden MDR-TB countries by subregion are shown in Table 1. MDR-TB rates among new and previously treated cases are significantly higher in these countries than in the top three high MDR-TB burden countries in other WHO regions. In 2012, the highest rates were in Belarus, where respectively 35% and 69% of new and previously treated cases were estimated to have MDR-TB.[15] A drug resistance survey conducted in 2010–2011 in Belarus found that respectively 32.3% and 75.6% of new and previously treated patients had MDR-TB, of which 12% had XDR-TB.[20]

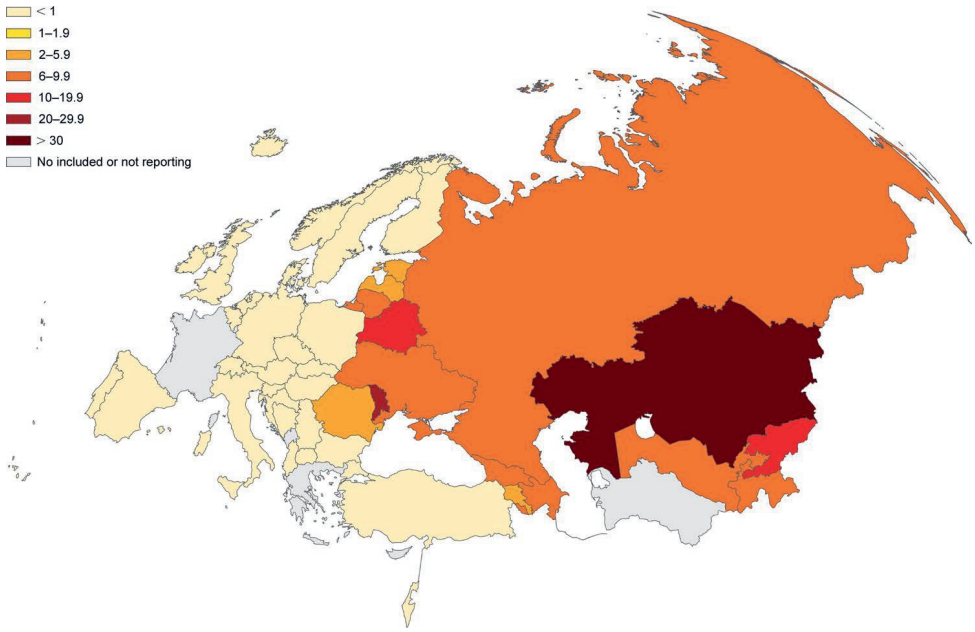

Figure 1. Notification rates of MDR-TB cases/100 000 population, European Region, 2012 (reproduced with permission from Tuberculosis Surveillance and Monitoring in Europe 201411). MDR-TB = multidrug-resistant tuberculosis.

XDR-TB accounts for approximately 9% of drug-resistant cases, with the majority also occurring in the region's 15 high-burden countries.[15] However, the added burden of pre-XDR-TB, defined as MDR-TB plus resistance to either a fluoroquinolone or a second-line injectable, is much higher. A recent study utilising regional data found that of those MDR-TB patients who underwent second-line drug susceptibility testing (DST), a total of 41.1% (95% confidence interval [CI] 32.3–50.0) had resistance to either a fluoroquinolone or a second-line injectable agent or both (i.e., either pre-XDR or XDR-TB).[21] Concurrently, among new and previously treated cases, MDR-TB treatment success rates have decreased from respectively 72.5% and 50% in 2005 to 66.1% and 46.5% in 2010.[15,22] In

total, only 49% of people diagnosed with MDR-TB had a successful treatment outcome, well below the 75% target. [15,16] Despite these trends in treatment success, there has been a steady decline in mortality rates from TB since 2002, also in line with the MDG targets. The estimated mortality for 2012 was 3.9 per 100 000 population (95% CI 3.8–4.0) in the region, corresponding to approximately 35 000 deaths.[15]

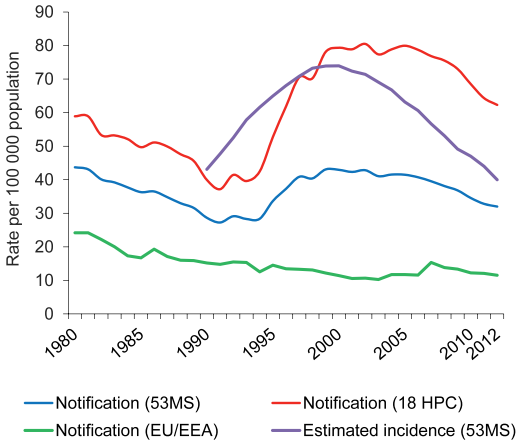

Figure 2. TB notification rate and estimated incidence in the WHO European Region, 1980–2012. MS = Member States (53 in the WHO European Region); HPC = high-priority countries (i.e., high MDR- and XDR-TB burden countries in the WHO European Region, plus Bulgaria, Romania, Turkey and Turkmenistan); EU = European Union; EEA = European Economic Area; MDR-TB = multidrug-resistant tuberculosis; XDR-TB = extensively drug-resistant TB.

The burden of MDR- and XDR-TB in eastern european countries

Ten of the European Region's high MDR-TB burden countries are in Eastern Europe (Figure 1, Table 1). The TB incidence rate has been falling in most Eastern European countries, except for Azerbaijan and Ukraine.[15] Utilising national data routinely reported to the WHO,[15] trends in the proportion of MDR-TB among all notified TB cases (new and previously treated) with first-line DST plotted against treatment success rates for each of these countries are shown in Figure 3. It should be noted that year-to-year trend assessments may not be reliable in some cases, given overlapping CIs; however, observations from reported surveillance data are nonetheless described.

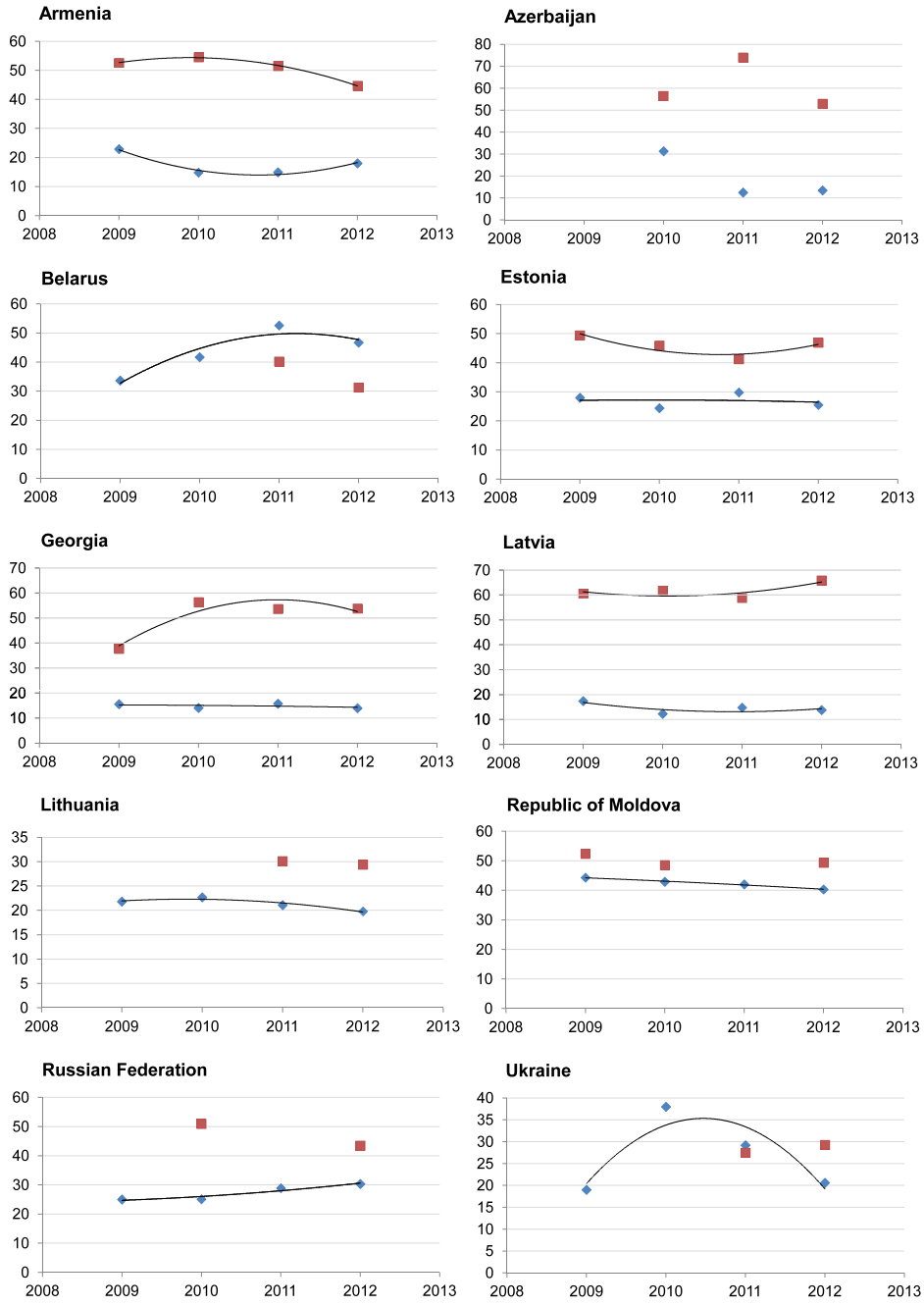

Figure 3. Proportion of MDR-TB among all notified TB cases with first-line DST and treatment success rates in countries in Eastern Europe, 2009–2012. Note: Trend-line not drawn where fewer than 4 data points are available. x-axis = year; y-axis = proportion; ♦ = proportion of MDR-TB among all notified TB cases with firstline DST; ■ = proportion of all notified MDR-TB cases with a successful treatment outcome for that year. MDR-TB = multidrug-resistant tuberculosis; DST = drug susceptibility testing.

Of the countries that have universal or near universal (95%) first-line DST coverage among bacteriologically confirmed TB cases (Armenia, Belarus, Estonia, Georgia, Latvia, Lithuania and the Russian Federation), the proportion of MDR-TB appears to have largely levelled off, with the exception of Belarus. The Russian Federation has also experienced a slight but steady increase in MDR-TB since 2009. However, given the large population size of the country, and therefore the number of TB cases (Table 1), even a slight increase in the proportion of MDR-TB represents a large absolute number of cases. Data from the country are, however, only available and reported on a subnational level from certain geographic areas; the currently known burden of MDR-TB may therefore not be representative of the entire country.[21]

Table 1. Estimated annual incidence of MDR-TB and estimated proportion of new and previously treated TB cases with MDR-TB among all notified TB cases in the 15 high MDR- and XDR-TB burden countries and high-priority countries in the WHO European Region, compared to the top three high MDR- and XDR-TB burden countries in other WHO Regions in 2012

	Estimated annual incidence of MDR-TB	Estimated % of TB cases with MDR-TB of total notified	
	Cases n (95%CI)	Newly treated % (95%CI)	Previously treated % (95%CI)
High MDR-TB burden and high-priority countries in the WHO European Region			
High MDR-TB burden countries in Eastern Europe			
Armenia	250 (220–280)	9.4 (7.0–12)	43 (38–49)
Azerbaijan	2 800 (2 600–3 000)	22 (19–27)	56 (50–62)
Belarus	2 200 (2 100–2 200)	35 (33–37)	69 (66–71)
Estonia	70 (56–85)	20 (14–26)	50 (35–65)
Georgia	630 (570–690)	9.2 (7.9–11.0)	31 (27–35)
Latvia	120 (100–140)	11 (8.8–14)	32 (23–42)
Lithuania	300 (270–330)	11 (9.5–14)	44 (39–49)
Republic of Moldova	1 700 (1 600–1 800)	24 (21–26)	62 (59–65)
Russian Federation	46 000 (43 000–49 000)	23 (21–25)	49 (44–53)
Ukraine	6 800 (6 500–7 000)	14 (14–15)	32 (31–33)
High MDR-TB burden countries in Central Asia			
Kazakhstan	7 000 (6 900–7 200)	23 (22–24)	55 (54–56)
Kyrgyzstan	1 800 (1 600–2 000)	26 (23–30)	68 (65–72)
Tajikistan	910 (800–1 000)	13 (9.8–16)	56 (52–60)
Uzbekistan	4 000 (3 700–4 300)	23 (18–29)	62 (52–71)
High-priority countries in the WHO European Region			
Bulgaria	100 (78–130)	2.3 (1.3–3.8)	23 (17–31)
Romania	800 (610–980)	2.8 (1.8–4.2)	11 (8.0–15)
Turkey	520 (460–580)	3.2 (2.7–3.7)	22 (19–25)
Turkmenistan*		3.8 (1.1–9.5)	18 (11–27)
High MDR-TB burden countries in other WHO regions (top 3)			
India	64 000 (49 000–79 000)	2.2 (1.9–2.6)	15 (11–19)
China	59 000 (52 000–66 000)	5.7 (4.5–7.0)	26 (22–30)
Philippines	12 000 (9 300–15 000)	4.0 (2.9–5.5)	21 (14–29)

* No data reported for the estimated annual incidence of MDR-TB.
MDR-TB = multidrug-resistant tuberculosis; XDR-TB = extensively drug-resistant TB; WHO = World Health Organization; CI = confidence interval.

Table 2. Proportions of pre-XDR-TB and XDR-TB among countries in Eastern Europe[17]

		MDR-TB cases with second-line DST	Resistance to a fluoroquinolone	Resistance to a second-line injectable agent	XDR-TB
Country*	**Year**	**results**	**n (%)**	**n (%)**	**n (%)**
Armenia	2007	199	25 (12.6)	—	10 (5.0)
Azerbaijan (Baku City)	2007	431	125 (29.0)	—	55 (12.8)
Belarus	2011	612	128 (20.9)	235 (38.4)	73 (11.9)
Estonia	2012	55	12 (21.8)	10 (18.2)	4 (7.3)
Georgia	2012	341	51 (15.0)	149 (43.7)	30 (8.8)
Latvia	2012	106	21 (19.8)	61 (57.5)	17 (16.0)
Lithuania	2012	210	68 (32.4)	90 (42.9)	52 (24.8)
Russian Federation (Tomsk Oblast)	2005	201	—	—	11 (5.5)

* No data available for the Republic of Moldova or Ukraine.
XDR-TB = extensively drug-resistant tuberculosis; MDR-TB = multidrug-resistant tuberculosis; DST = drug susceptibility testing; — = none reported.

In some countries, as the absolute number of TB cases continues to decrease, so too has the number of MDR-TB cases. Countries that have experienced a levelling-off or a reduction in the proportion of MDR-TB (Armenia, Estonia, Georgia, Latvia and Lithuania) may represent a success in the control of MDR-TB, given the decreasing TB incidence rate and universal DST coverage in these countries; however, data on early deaths that may occur before notification are not available. While the proportion of MDR-TB in the Republic of Moldova and Ukraine also appears to have decreased, first-line DST coverage in these countries is below 80%; the true rates of MDR-TB may therefore be greater than currently reported. Trends in Azerbaijan are also difficult to interpret, as DST coverage is below 80% in the country and no data were reported for 2009.

The decreasing treatment success in MDR-TB patients is a continuing problem. Georgia experienced an increase in treatment success rates from 2009 to 2010, which has since levelled off. The rate in Latvia has remained relatively stable, with an increase in 2012 over the previous year. Estonia also experienced an increase in 2012 over the previous year; however, this is after a downward trend since 2009. Critically, apart from a few subsettings, including penitentiary services in Azerbaijan, none of the 10 Eastern European countries have reached the WHO target of a 75% treatment success rate. Contributing to this problem are substantial levels of additional drug resistance and XDR-TB (Table 2).[21,23,24]

The countries with the highest mortality rates due to TB in the WHO European Region (and the eastern European subregion) are the Republic of Moldova (18 cases/100 000), the Russian Federation (13/100 000) and Ukraine (also 13/100 000).[15] These rates are well

above both the estimated mortality rate for the region and the mortality rate for the European Union/European Economic Area, which is below 1 case/100 000.

Progress in MDR-TB control in Eastern Europe

Much progress has been achieved in efforts to control TB in Eastern Europe since the implementation of the Action Plan in 2011. A complete review of national programmatic advances as a result of the Action Plan is beyond the scope of this review. However, several large initiatives have been implemented at regional level, including in Eastern Europe, in response to the MDR- and XDR-TB crisis.

All countries in Eastern Europe have developed national MDR and XDR-TB response plans in consultation with the WHO. These plans are based on country TB drug resistance surveys, resource availability, human immunodeficiency virus (HIV) burden and other national contexts.[25] Several technical advisory mechanisms have also been established in the region to achieve the comprehensive goals of the Action Plan and national MDR- and XDR-TB response plans. These mechanisms include the Green Light Committee/ Europe (GLC/Europe), an independent technical advisory body to support countries with state-of-the-art clinical advice and to scale up programme management of MDR- and XDR-TB;[26] the European Respiratory Society-WHO Electronic Consilium (consilia are multidisciplinary teams of specialists organised to give expert clinical consultation for MDR- and XDR-TB and other difficult- to-treat TB cases, such as TB-HIV and paediatric cases);[27] the European Tuberculosis Laboratory Initiative (ELI) to improve and expand second-line DST and scale up diagnostic capacity, including the use of rapid molecular tests such as Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA);[28] and the Regional Interagency Collaborating Committee on TB Control (RCC-TB), to improve partnerships and strengthen coordination among partners.[29]

Ongoing monitoring and evaluation will reveal the full impact of the Action Plan including these initiatives and others on the control of MDR-TB in the Region. However, several indicators of overall progress are already evident, such as the reduction in TB incidence rates and stabilisation of MDR-TB rates in many of the countries in the Eastern European subregion. In addition, treatment coverage for MDR-TB patients increased from 63% of estimated MDR-TB patients in 2011 to 96% in 2013.[25] Extensive progress has also been made in the coverage and quality of TB surveillance. Since 2010, nationwide representative data on levels of MDR-TB in Belarus, and now Azerbaijan (in addition to other countries in the WHO European Region), have been made available through nationwide drug resistance surveys.[20,21,30]

Challenges remaining

Despite progress and good impetus in efforts to control MDR-TB rates in Eastern Europe in recent years, critical challenges remain. These challenges are most often interconnected and multifaceted; in addition, some are highly specific to the country context, while others are apparent throughout Eastern Europe and all high-burden countries in the WHO European Region. While not intending to be an exhaustive list, some of the most critical of these latter challenges are discussed below.

MDR-TB with additional resistance

The high levels of pre-XDR-TB and XDR-TB in Eastern Europe (Table 2) are of great concern. Despite widespread coverage of second- line drugs, there is still inadequate treatment and insufficient patient support mechanisms in some Eastern European countries, including some member states of the European Union.[25] Evidence of this is seen in projects that are not supported internationally by technical agencies such as the WHO or the GLC, where treatment success among MDR-TB patients is extremely low (28% in some settings).[31] This is mainly due to incomplete treatment regimens and lack of full access to all necessary second-line anti-tuberculosis drugs. Adverse drug events leading to poor treatment adherence during the long course of MDR- and XDR-TB treatment also severely compromise treatment success.[32] Despite the recent conditional approval of two new medicines (bedaquiline and delamanid) by the international drug regulatory authorities, their full-scale use is not in place, as there is a need for the establishment of strong pharmacovigilence systems.

Patient hospitalisation

Contributing to the spread of drug-resistant forms of TB, some countries hospitalise patients unnecessarily while awaiting DST results or during the intensive phase of drug-susceptible anti-tuberculosis treatment.[33–38] Ambulatory services and other models of care, including home-based treatment, are not fully functional in these countries.[25] In the absence of adequate airborne infection control, hospitalisation can lead to nosocomial transmission to health care workers, ancillary staff and other patients, and secondary infection with MDR- or XDR-TB strains.[39] A recent meta- analysis found no difference in treatment outcomes of patients treated in ambulatory vs. hospitalised settings, and the WHO currently recommends minimising unnecessary hospitalisations and using ambulatory rather than hospital-based models of care for MDR-TB treatment.[11] This is also likely to be much more acceptable to patients in the longer term.

Rapid diagnostics for first-line DST

New rapid molecular tests for MDR-TB, such as Xpert, play a vital role in the rapid identification and control of drug-resistant TB:[40] in theory, the quicker the detection of drug-resistant strains, the faster patients can be initiated on appropriate treatment

regimens, thereby minimising the window of transmission, although this also depends on good linkages and referral systems to care. Rapid diagnostic technologies, however, are not yet universally available in all Eastern European countries.[16,32,41] Reduced funding due to the financial crisis in some countries has also exacerbated the difficulties in scaling up diagnostic capacities, including the use of molecular tests and improving biosafety.

Second-line DST and surveillance

Data on second-line DST are still limited, and electronic data management is lacking in many countries in Eastern Europe, adding to difficulties in analysing programme performance.[25] Some countries in Eastern Europe collect second-line anti-tuberculosis drug resistance data only during subnational surveys, which are not repeated, while other countries have limited or no data.[21] Rapid second-line DST is essential so that treatment can be adapted to resistance patterns in a timely manner. However, only Armenia, Georgia and Latvia currently have universal or near universal coverage of second-line DST.[15]

Vulnerable populations

Another serious challenge to MDR- and XDR-TB control is reaching vulnerable populations such as children, migrants, prisoners and people living with HIV, who are at greater risk for contracting and developing MDR- or XDR-TB.[42] Considerable efforts have been made on this front since 2011, with the development of a minimum package for cross-border TB control and care in 2012,[43] and in 2013 the International Union Against Tuberculosis and Lung Disease (Paris, France), the WHO and other international stakeholders issued an official statement of 12 action points to improve TB prevention and control in prisons.[44] However, many countries in Eastern Europe have yet to implement the recommendations put forth in these statements.

Children

Children are often a neglected and vulnerable group with regard to MDR- and XDR-TB. This is due to the low number of bacilli in sputum among children,[45] which makes TB, MDR- and XDR-TB harder to diagnose with sputum smear microscopy, culture and molecular tests.[46] In 2011, only approximately 4% of the estimated cases of childhood TB in the 10 high-burden Eastern European countries were detected and reported,[45] and reporting on paediatric MDR- and XDR-TB is currently very limited. WHO guidelines on childhood TB, including paediatric diagnostics and drug formulations, have recently been updated;[47] however, these need to be adopted into national strategic TB plans and practice in Eastern Europe.

Migrants

Migrants often face a myriad of challenges such as discrimination, economic adversity, language barriers, stigma and fear of deportation. [48] These challenges, combined with the

migratory nature of the population, pose enormous barriers and difficulties in accessing diagnosis and continuous anti-tuberculosis treatment services.[48] Both internal and cross-border migration enhance TB transmission. Many migrants also live in close proximity with family members or other individuals, as is the case with refugees and seasonal migratory workers living in temporary housing. All of these factors increase the risk of developing, contracting and transmitting drug-resistant forms of TB. Complicating the situation, some countries in both Eastern and Western Europe deport migrants with TB without considering the public health and human rights issues involved, or without taking adequate infection control measures, thereby increasing the risk of cross-border transmission.[43,49] Levels of migration vary substantially across Eastern Europe, as do reported rates of TB among migrants; in 2010, 2.4% of notified TB cases in Lithuania were foreign-born, compared to 17.6% in Estonia.[50] In the Russian Federation in 2011, less than 5% of notified cases were reported as foreign-born through routine surveillance; however, an earlier study from 2005 found that 26.9% of detected TB cases in Moscow were among migrants.[51]

Prisoners

Similar to migrants, incarcerated patients have a much higher risk for developing or contracting drug-resistant TB compared to the general population. In 2011, the pooled rate of TB in prisons (from all reporting sites) in the Russian Federation was 14 times that of the general population. Rates in Azerbaijan and Georgia were respectively 23 and 26 times higher in prisons than in the general population.[15] Prisons in Eastern Europe are often poorly ventilated and crowded, and incarcerated patients spend long periods of time in these environments.[52] Other determinants are high rates of HIV infection, injecting drug use and poor nutritional status.[44] Human and financial resources for TB and MDR-TB prevention and control in prison are often scarce in Eastern Europe, and there are still gaps in coordination between civilian and penitentiary TB services.[25] There are, however, recent best practice examples of TB and MDR- and XDR-TB control in the Azerbaijan prison sector, and effective continuity of TB care for released prisoners in Azerbaijan and the Republic of Moldova,[53] which should be scaled up in the region.

Persons living with HIV

Individuals living with HIV are highly susceptible to TB,[54] and Eastern Europe has one of the fastest growing HIV epidemics in the world.[55] Approximately 65% of new HIV infections in the region in 2010 occurred in the Russian Federation and Ukraine.[56] These countries also had the highest rates in the region in 2011, with respectively 44 and 36 cases per 100 000 population.[56] Most countries, however, lack a functioning TB-HIV coordinating mechanism to facilitate the delivery of integrated TB and HIV services, including those related to narcology services for those with drug or alcohol dependency.[25]

Human resources

Lack of human resources is an important challenge that affects all levels of MDR- and XDR-TB prevention control and care in Eastern Europe. There is particular need for specialised human resources to manage cases of drug-resistant TB in both children and adults, deliver adequate services for case detection and scale up diagnostic and laboratory capacity.[25,57]

Funding

In 2011, there was a considerable projected funding gap of over 60% to fully implement the Action Plan for M/XDR-TB in the European Region.[16] This funding gap has still not been met. In countries financially supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund, Geneva, Switzerland), the treatment success rate among MDR- and XDR-TB patients is 78% compared to 20% in other settings without Global Fund support. 58 This is strong evidence of the need for funding from The Global Fund and other international donor agencies to address the current challenges to MDR- and XDR-TB control. A critical challenge in Eastern Europe will be the gradual shift in funding to national mechanisms, which is a requirement under The Global Fund's New Funding Model, and to ensure that progress is not lost due to financial gaps.

Ways forward

The 2015 MDG deadline is fast approaching, as are the deadlines for the Global Plan to Stop TB and the Consolidated Action Plan for M/XDR-TB in the European Region. In response to this, and the continuing challenges facing the control of TB and MDR- and XDR-TB, an ambitious Post-2015 Global TB Strategy has recently been developed by the WHO and approved by the World Health Assembly.[59] The strategy, which has several milestones for 2025 and 2035, comprises three main pillars summarised in Table 3. It is imperative that the Post-2015 Global TB Strategy be adapted to regional and country-specific contexts so that there is a framework for continued efforts to prevent and combat TB and MDR and XDR-TB, and that there is a seamless transition between preand post-2015 plans. This is particularly the case in Eastern Europe and the WHO European Region as a whole, which has the world's largest proportion of high MDR- and XDR-TB burden countries.

In Eastern Europe, as *M. tuberculosis* strains resistant to firstand second-line drugs increasingly replace drug-susceptible strains, TB cases will become increasingly difficult to treat. This may already explain the falling treatment success rates seen across the region. In line with the current regional Action Plan and the post-2015 Global Strategy, several immediate actions are needed to address the challenges to MDR- and XDR-TB control in Eastern Europe. First, to address the spread of primary infection with drug-resistant strains of *M. tuberculosis*, improved infection control is needed. In line with this, it is essential that hospital financing mechanisms be revised to promote free ambulatory care instead of a 'fee-per-bed' policy, which promotes hospitalisation and ongoing transmission of drug-

resistant TB.[60,61] A new vaccine is also needed. Second, to address acquired resistance, prompt and improved treatment is necessary. Full access to all necessary second-line anti-tuberculosis drugs needs to be ensured. In addition, emphasis should be placed on shorter and more effective treatment regimens and psychosocial support mechanisms to improve adherence in the face of adverse side effects. Countries should make particular effort to address populations and projects that are not supported by technical agencies such as the WHO and GLC. Bedaquiline and other new TB medicines also need to continue to be developed urgently and introduced under specific conditions, such as compassionate use and with special attention to pharmacovigilance. To guard against resistance to these new drugs, it is critical that international regulations on their use be strengthened, and that availability of drug regimens be ensured so that drug stockouts and subsequent misuse of new drugs be prevented. Third, and vital to curbing both routes of infection with drug-resistant TB, is early and rapid detection. Central to this is strengthening laboratory capacity to improve the use of current rapid diagnostics and second-line DST. In addition, there is a need for improved, easily applicable and affordable molecular tests in high-burden areas. Fourth, vulnerable populations are at highest risk for contracting or developing MDR- and XDR-TB, and also pose a risk for transmitting and sustaining disease transmission if not properly treated. If an end to the TB epidemic is to be realised, MDR- and XDR-TB among vulnerable populations should be addressed urgently.

A longer-term approach to addressing MDR- and XDR-TB among vulnerable populations, and in line with Pillars 1 and 2 of the Post-15 Global TB Plan, is strengthening the health systems.[62] This implies a move away from vertical TB service delivery mechanisms, which are often difficult for vulnerable populations such as migrants and persons living with HIV to access or to receive appropriate care, to a coordinated/integrated health care system adapted to client needs. This approach would need intensified collaboration and joint action by HIV and TB control programmes. In addition, such a model would enable greater emphasis to be placed on social determinants of health, such as poor living and working conditions, HIV infection, malnutrition, smoking, diabetes and drug and alcohol use disorders, which are major drivers of the TB and MDR- and XDR-TB epidemic.[42,63,64] A health systems approach could also alleviate the challenge of specific human resources and financing currently needed for TB services. Great care must be taken, however, for health systems strengthening to be implemented cautiously, systematically and with appropriate financial backing to avoid suboptimal hastily introduced health care reforms, which could have a negative effect on TB programmes.[57]

Pillar 3 of the Post-15 Global TB Plan will also play a critical role in the future of MDR- and XDR-TB control. One third of the population is estimated to be latently infected with TB; as long as there is latent tuberculous infection, there is the possibility of the development and transmission of TB disease. If the vision of the Post-15 Global TB Strategy is to be met,

there is an urgent need for research and development on vaccines and new medicines for TB, MDR- and XDR-TB. In addition to basic sciences research, there is also a need for operational research. The role of operational research has been successfully and extensively demonstrated in numerous settings.[4,65–67] Through surveillance and routine data collection, it is currently possible to understand the burden and trends in TB and MDR- and XDR-TB, although improvements in reporting are needed. It is envisaged that the operational research agenda will be greatly strengthened and expanded under Pillar 3; this should have an enormous impact on improving programme performance and serve as an evidence base for policy and practice.

Table 3. Post-2015 global tuberculosis strategy framework (reproduced with permission from the draft global strategy and targets for tuberculosis prevention, care and control after 2015 (A67/11)[59]

Vision	A world free of TB – Zero deaths, disease and suffering due to TB
Goal	End the global TB epidemic
Milestones for 2025	75% reduction in TB deaths (compared with 2015) 50% reduction in TB incidence rate (<55 TB cases/100 000) – No affected families facing catastrophic costs due to TB
Targets for 2035	95% reduction in TB deaths (compared with 2015) 90% reduction in TB incidence rate (<10 TB cases/100 000) – No affected families facing catastrophic costs due to TB
Principles	
1 Government stewardship and accountability, with monitoring and evaluation 2 Strong coalition with civil society organisations and communities 3 Protection and promotion of human rights, ethics and equity 4 Adaptation of the strategy and targets at country level, with global collaboration	
Pillars and components	
1 Integrated, patient-centred care and prevention A Early diagnosis of TB, including universal drug susceptibility testing; and systematic screening of contacts and high-risk groups B Treatment of all people with TB, including drug-resistant TB, and patient support C Collaborative TB-HIV activities and management of comorbidities D Preventive treatment of persons at high risk, and vaccination against TB 2 Bold policies and supportive systems A Political commitment with adequate resources for TB care and prevention B Engagement of communities, civil society organisations, and public and private care providers C Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control D Social protection, poverty alleviation and actions on other determinants of TB 3 Intensified research and innovation A Discovery, development and rapid uptake of new tools, interventions and strategies B Research to optimise implementation and impact, and promote innovations	

Conclusion

The burden of MDR- and XDR-TB in Eastern Europe is high. While much progress has been made in controlling drug-resistant TB since the launch of the Consolidated Action Plan in 2011, the prevalence of second-line drug resistance has severely threatened treatment

success and continued progress in controlling MDR and XDR-TB in Eastern Europe. While mortality rates do not appear to have been affected yet, vigilance and intensified efforts are needed as we head into 2015 if decreasing mortality rates are to be kept on track. There are several current challenges in MDR-TB and XDR-TB control in Eastern Europe as regards access to appropriate treatment regimens, patient hospitalisation, scale-up of laboratory capacity, including the use of rapid diagnostics and second-line DST, vulnerable populations, human resources and TB financing.

Solutions to these challenges are aligned with the Post-2015 Global TB strategy. As a first step, the global TB strategy must be adapted at regional and country levels to serve as a framework for immediate actions as well as ways forward in the longer term. Longer-term solutions include strengthening health systems as a way to ensure adequate TB care for vulnerable populations and to address social determinants of health, which are drivers of the TB epidemic.[42] In addition to initiatives and continued efforts under Pillars 1 and 2 of the Post-2015 Global TB Strategy, Pillar 3, research, will play a critical role in achieving a vaccine and new medicines for MDR- and XDR-TB, improving TB programme performance and creating an evidence base for effective policy as we head into a new era of TB control.

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CHAPTER 6

6

Bacille Calmette–Guérin vaccination: the current situation in Europe

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Tuberculosis is a major public health priority. This is not only because of its daunting morbidity and mortality rates, both globally and in Europe (summarised in figs 1 and 2) [1, 3–5], but also because of the natural history of the disease. Active (contagious) tuberculosis disease occurs after a period of latency (or subclinical infection), and different risk factors [6–13], in combination with latent infection, introduce challenges to prevention, diagnosis and treatment of the disease. Vaccination against tuberculosis, if effective, would be therefore critical to control and elimination strategies [14–16]. The bacille Calmette– Guérin (BCG) vaccine is, from a historical perspective, a milestone of tuberculosis control (figs 3–7). During the first half of the 20th century, it was administered ubiquitously throughout Europe, but is now recommended by the World Health Organization (WHO) to be given once at birth, specifically in tuberculosis-endemic areas.

The BCG is currently the only available vaccine to provide protection against haematogenous spread and subsequent severe clinical forms of tuberculosis, including meningitis [17–19]. It is included in national childhood immunisation programmes in most high-burden countries in Europe, and is also administered to high-risk populations in nonendemic areas [17]. In western Europe, as in other low-incidence regions, discontinuation of national BCG vaccination began following initial pilot studies in the former Czechoslovakia (1961–1972) and Sweden (1975) [20–22]. These studies demonstrated the decline in risk of serious forms of tuberculosis in children, evidence of the weak protective effect of BCG in adults and lack of impact on the global incidence of tuberculosis. Usage of BCG by country in the WHO European Region is summarised in table 1.

Given that a more effective vaccine against tuberculosis does not currently exist [26], BCG remains an important prevention tool, particularly in children. Unfortunately, some countries have recently faced problems with adverse events (table 2) due to shifting from one strain of BCG to another [27]. Meanwhile, other countries are debating a shift away from national BCG vaccination to selective vaccination, although previous discontinuation experiences have produced transient increases in severe forms of tuberculosis, particularly tuberculous meningitis [20–22]. As countries weigh the impact of current and future BCG practices, guidance for BCG policy making is needed.

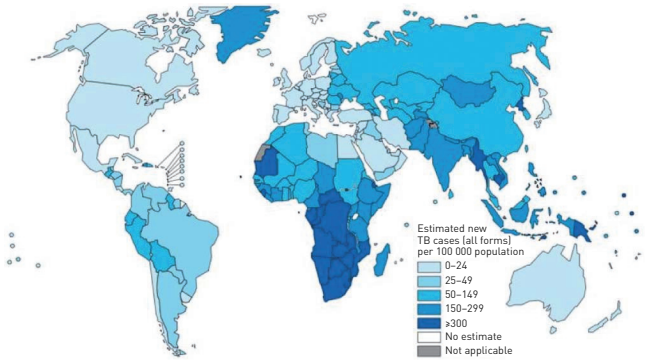

Figure 1. Global estimated TB incidence rates, 2011. Reproduced from [1] with permission from the publisher

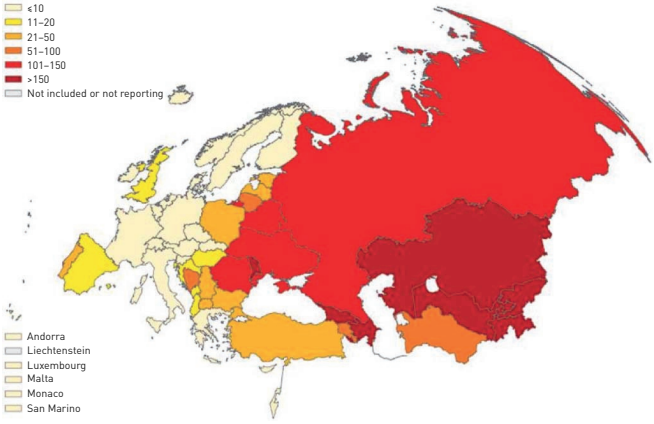

Figure 2. WHO European Region estimated TB incidence rates per 100,000 population, 2011*. Reproduced from [2] with permission from the publisher.

* Data from UN Administrated Province of Kosovo (in accordance with Security Council Resolution 1244 (1999)) is not included in the figures reported for Serbia

Figure 3. Wooden mask worn by health workers to announce a forthcoming vaccination campaign (Republic of Benin). Image courtesy of J.P. Zellweger.

The purpose of this editorial is to summarise current policy on administration and management of adverse events of the BCG vaccine from the WHO European regional perspective. The editorial will briefly summarise what the BCG vaccine is, the history of its development and production, its safety, as well as incidence and management of adverse events. Finally, it will provide guidance on BCG policy development.

The BCG vaccine and its history

The BCG vaccine provides protection against severe forms of tuberculosis, particularly tuberculous meningitis and disseminated tuberculosis in infants and young children [17–19]. It does not prevent primary infection and, more importantly, it does not prevent reactivation of latent pulmonary infection, the principal source of spread of *Mycobacterium tuberculosis* in the community. The impact of BCG vaccination on transmission is therefore limited.

BCG contains a live, attenuated strain of *Mycobacterium bovis*, which primarily causes tuberculosis in cattle. *M. bovis* was originally isolated in 1908 from a cow with bovine

tuberculosis by Calmette and Guérin at the Pasteur Institute in Lille, France. In order to attenuate the strain, it was carefully subcultured every 3 weeks for ,13 years. During this time, many genetic changes (or point mutations) occurred making the strain less virulent in animals such as cows and guinea pigs. The resulting altered strain was named BCG. After extensive safety testing in animals, BCG was first used as a vaccine in human infants in 1921 [18]. The vaccine was used extensively and for many years, as there were no other treatment options against tuberculosis until the development of isoniazid in the 1940s, and confidence in the preventive effect of BCG vaccination was high both in the medical and the patients' communities (figs 3–7).

Today, there are several different substrains of the original BCG strain. The reason for this is that during the early years of the vaccine, all BCG cultures were maintained at the Pasteur Institute in Paris, France (fig. 5). However, from 1924 to 1931, the BCG strain was distributed to several laboratories throughout the world where they were maintained by continuous subculture [18, 28]. After many years, it became clear that the various strains maintained in different laboratories were no longer identical to each other. Indeed, it is likely that all the various strains maintained by continuous subculture continued to undergo genetic changes. Even the original BCG strain maintained in Paris continued to change during the subculturing needed to maintain the viability of the strain. To limit these genetic mutations, procedures used to maintain the strains were modified. Today, the strains are maintained using a seed lot production technique to limit further genetic variation using lyophilised cells so that each batch starts with the same substrain [18, 29].

Figure 4. "To defeat tuberculosis is easy with the BCG". Advertisement in a peripheral TB dispensary, dating from the time of French colonization, about 1950 (Republic of Benin). Image courtesy of Jean Pierre Zellweger

BCG production and substrains

The BCG vaccines that are currently in use are produced at 40 sites throughout the world [29], many for local use within the country of production. These vaccines are not identical. Some differences in molecular and genetic characteristics are known; however, the extent to which they differ in efficacy and safety in humans is not clear [18, 29]. Globally, the most widely used BCG vaccine substrains include Connaught, Danish, Glaxo, Moreau, Moscow, Pasteur and Tokyo [28]. In high-incidence eastern European countries and former Soviet states, the predominant substrain is BCG Moscow. Although BCG Danish and Pasteur have been found to be more immunogenic [27], greater efficacy of these strains has not been demonstrated in field trials [30]. Therefore, there are currently no recommendations advising the use of one strain over another [29].

Although there are no formally recommended vaccines, ,25% of the world supply of BCG is purchased by the United Nations (UN) Children's Fund and other UN agencies for distribution to developing countries [29]. These substrains are purchased according to a WHO pre-qualification process, which determines their eligibility for use in national immunisation programmes (table 3) [31]. Vaccines are added to the prequalification list after extensive quality control evaluations and manufacturing site audits performed by the WHO. The list is not exhaustive, and the fact that certain BCG substrains are not included in the list does not mean that, if evaluated, they would not be found to comply with pre-qualification standards and operational specifications.

Figure 5. French Ministry of Health educational poster supporting BCG vaccination. Image courtesy of J.P. Zellweger

Safety

The BCG vaccine is the oldest vaccine still in use. It has been administered to .4 billion people worldwide since 1921 [18, 28, 29] and the risk of adverse events has generally been considered to be low. Recently, however, it has been found that use of the vaccine in persons who are immunocompromised (such as those with HIV) may result in an infection caused by the BCG itself [18, 32, 33]. As BCG is a live vaccine, there is an increased risk of mycobacterial circulation in the absence of a competent immune response. This can lead to disseminated BCG disease [34]. There is also concern that BCG vaccination may accelerate HIV disease progression amongst HIV-infected infants by triggering an immune response that leads to the spread of the virus [35]. In addition, even among immunocompetent persons, local reactions, including ulceration at the site of vaccination, may result in shedding of live organisms, which could, in turn, infect others who may be immunocompromised.

Figure 6. Tuberculosis/HIV-infected children in Myanmar.
2012 Matthieu Zellweger (with AIDSpartners.org)/ matthieuzellweger.com

Figure 7. Romania, 1974. Six-year-old children are re-vaccinated against tuberculosis (according to the guidelines available at the time; at present no evidence of any protection of re-vaccinating with BCG is available, so re-vaccination is not recommended by WHO). WHO image, courtesy of the United States National Library of Medicine, History of Medicine Division.

WHO position on BCG vaccination

The core WHO policy recommendations are summarised in table 4. Currently, the WHO position is that a single dose of BCG vaccine should be given to all infants as soon as possible after birth in countries with a high burden of tuberculosis > 40 cases per 100 000 population). Contraindications are infants or persons known to have HIV or other immunosuppressive conditions (fig. 6) [35, 36]; in settings with adequate HIV services, BCG vaccination should be delayed for infants born to mothers known to be infected with HIV until these infants are confirmed to be HIV negative. Although BCG might be potentially useful in other groups (*e.g.* health care workers, travellers to endemic areas and contacts of multidrug-resistant cases) the available evidence is not sufficient to recommend its use. The WHO does not recommend BCG revaccination as there is little or conflicting evidence of whether this confers additional protection, and revaccination may increase the risk for adverse events.

Adverse events

Amongst immunocompetent infants and children, mild events such as localised skin reactions following BCG vaccination are common; almost all recipients of BCG develop a bluish-red pustule accompanied by pain, swelling and erythema within 2–4 weeks after vaccination [37, 38], with ulceration and drainage in 70% of vaccinated individuals [29, 30]. Abscess and regional lymphadenitis occur in 1–2% of vaccinated individuals [29, 39]. Severe adverse events occur very rarely. The absolute risks of severe adverse events are summarised in table 2. Importantly, although there are currently no recommendations for the use of certain strains, the Pasteur and Danish strains are known to induce more adverse reactions [30, 38, 40].

Among HIV-infected or other immunocompromised infants and children, the absolute risk of severe adverse events from BCG vaccination has been found to be hundreds of times higher compared to immunocompetent children. Rates of disseminated BCG disease are estimated to approach 1% of HIV-infected infants vaccinated with BCG [41] and has an all-cause mortality rate of 75–86% [32–34, 42]. Additionally, BCG immune reconstitution inflammatory syndrome occurs in up to 15% of HIV-infected children who receive the BCG vaccine [32–34, 43].

Table 1. BCG Vaccination in the WHO European Region. Countries listed in alphabetical order and according to TB priority (56–58). (4)

WHO European Region, High-Priority TB Countries			
Country	**General BCG at birth (Entire country)**	**Revaccination**	**Selective vaccination**
Armenia	Birth		
Azerbaijan	4-7 days		
Belarus	3-5 days	Revaccination performed at 7 years (in children from a TB contact, in social risk groups, without a visible BCG scar, and handicapped children without specific contraindications for live vaccines)	
Bulgaria	Birth	7 months; 7, 11, 17 years (after Mantoux test negative)	
Estonia	1-5 days		
Georgia	0-5 days		
Kazakhstan	Birth	6 years (after Mantoux test negative)	
Kyrgyzstan	Birth		
Latvia	2-5 days		
Lithuania	3 days		
Republic of Moldova	2 days	6-7 years (after Mantoux test negative)	
Romania	Birth		
Russian Federation	3 days	7 (after Mantoux test negative), 14 years	
Tajikistan	3-5 days		
Turkey	2 months		
Turkmenistan	3 days	14 years (after Mantoux test negative)	
Ukraine	3-5 days	7 years (after Mantoux test negative during periods of TB epidemics)	
Uzbekistan	3-5 days		
WHO European Region, Non-high-Priority TB Countries			
Country	**General BCG at birth (Entire country)**	**Revaccination**	**Selective vaccination**
Albania	Birth		
Andorra	No		
Austria	No		Children, travellers and HCW at high and prolonged risk
Belgium	No		Children and HCW in prolonged exposure at high risk
Bosnia and Herzegovina	Birth		
Croatia	Birth		

Cyprus	No	Children with continuous contact with a contagious form of TB
Czech Republic	No	Children 6 months or older with TB in the family, contact with TB, origin or stay >3 months of the child or parents in a country with TB incidence > 40/100,000 or parental request
Denmark	No	Young children travelling for long periods of time to endemic areas, or living in Denmark in families with TB, or HCW caring for risk patients, and sometimes given to travelers to US due to US regulations
Finland	No[§]	TB in the family, parents originate from a country with high incidence, or moving to such country
France	No	Given at birth in Infants at risk (born in a country with a high prevalence of TB or with at least one parent born in such a country, or planning to stay at least one month in such a country, or with a history of TB in his/her family, or living in the Ile-de-France or French Guyana or Mayotte region, or any child considered by a physician as living in an environment with a high risk of exposure to TB) and professionals and students involved in health care, revaccination at entry if TST negative
Germany	No	
Greece	No[§]	
Greenland	Birth	
Hungary	Birth	
Iceland	No	
Ireland	Birth	
Israel	No	Newborns (BCG given at birth) and children with high risk, for example, babies from families that immigrated from endemic countries
Italy	No	HCW[¶]
Kosovo*		
Luxembourg	No	
Malta	No[§]	
Monaco	Birth	
Montenegro	Birth	
Netherlands	No	Children with one or two parents originating from high-incidence TB countries (BCG given at 5 months); Long-term travelers and expatriates to high-incidence TB countries

Norway	No		Newborns with parents from high prevalence countries and health/ birth professional students
Poland	Birth		
Portugal	Birth		
San Marino*			
Serbia	Birth		
Slovakia	No		
Slovenia	Birth		HCW, medical students, military (BCG given at start of work/ study)
Spain	No		Newborns in Basque country (País Vasco) (BCG given at birth), and children in close and long-term contact with smear positive adults; foreign-born children (< 5 years) returning to their country (high burden TB country) for more than 3 months; children (< 5 years) whose parents are working in high burden countries and have to stay with them more than 3 months
Sweden	No		Children born to parents from countries with a TB incidence >25 per 100 000 at the age of 6 months
Switzerland	No		Children at high risk of exposure (BCG given at birth)
The Former Yugoslav Republic of Macedonia	Birth	7 years	
United Kingdom of Great Britain and Northern Ireland	No		High risk areas (BCG given at birth)

§ General BCG vaccination performed after birth , at the age of: Finland>7 years; Greece 6 years; Malta 12 years
¶ Health workers at high risk
* No information

Management of adverse events

Management of local lymphadenitis remains controversial, with no consensus on the best strategy [29]. Treatment strategies range from observation (wait-and-see approach), to surgical drainage or resection, to treatment with antituberculosis drugs, to a combination of these approaches [29, 44]. In general, nonsuppurative BCG-induced lymphadenitis is a benign condition and regresses spontaneously without any treatment in 4–6 months [33]. For suppurative BCG lymphadenitis, needle aspiration is recommended in some countries, and may prevent discharge and associated complications such as fistulation. A common practice in many countries is direct injection or local instillation of antituberculosis drugs to the lesion; however, there is a poor quality of evidence to demonstrate a benefit from this practice [33], which might also promote drug resistance. Surgical incision is additionally not recommended for suppurative BCG lymphadenitis. Where needle aspiration has failed to relieve symptoms and suppurative nodes have already drained surgically or spontaneously with sinus formation, surgical excision is occasionally practiced, but carries additional risks associated with general anaesthesia needed for the procedure. Literature on the benefit of oral/systemic antituberculosis drug treatment without surgical drainage is conflicting, and a recent Cochrane review found no evidence of any benefit of using oral antibiotics to treat local or regional BCG-induced disease [33].

In general, oral antituberculosis medications should be reserved for infants developing rare systemic adverse reactions, such as disseminated BCG disease. In these cases, the criteria for *M. tuberculosis* should be used and the strain should be considered to be of intermediate susceptibility. Management should therefore include the appropriate combination of antituberculosis drugs; however, pyrazinamide should not be included in the drug regimen as all BCG strains have inherent resistance to this drug [29]. In addition, there is variable BCG resistance to isoniazid, which is one of the main antimycobacterial drugs available in tuberculosis-endemic settings, as well as possible acquired resistance to other first-line antituberculosis drugs [45–47]. Single-drug therapy, particularly with isoniazid, is therefore not recommended. It should also be noted that the clinical features of disseminated BCG disease are similar to those of severe tuberculosis, and sophisticated laboratory facilities may be needed to distinguish between *M. tuberculosis* and *M. bovis* BCG [42], as well as to test drug susceptibility.

Table 2. Summary of mild and severe adverse events*

Nature of Adverse event	Description	Rate/doses
Mild	Injection site papule (onset 2-4 weeks) Mild ulceration (1-2 months) Scar (2-5 months)	Almost all vaccinees
Severe	Local Local abscess Keloid Lymphadenitis Suppuration (onset 2-6 months)	1 per 1,000-10,000
	Systemic (1-12 months onset time)	
	Cutaneous skin lesions	Case reports only
	Osteitis	1 per 3,333-10[8]
	Disseminated BCG	1 per 230,000-640,000
	Immune Reconstitution Syndrome	1 per 640,000

From: Modified from WHO, Observed rate of vaccine reactions of Bacillus Calmette-Guérin (BCG) vaccine, April 2012(11)*

Table 3. Guidelines for BCG Vaccine

Guidelines for BCG Vaccine	
WHO	Revised BCG vaccination guidelines for infants at risk for HIV infection http://www.who.int/immunization/wer8221bcg_May07_position_paper.pdf Information Sheet, Observed rate of vaccine reactions of Bacillus Calmette-Guérin (BCG) vaccine, Apri http://www.who.int/vaccine_safety/initiative/tools/BCG_Vaccine_rates_information_sheet.pdf Prequalification of vaccines - further information http://www.who.int/immunization_standards/vaccine_quality/vq_index/en/index.html
CDC	Fact sheets, BCG Vaccine http://www.cdc.gov/tb/publications/factsheets/prevention/BCG.htm
The Union	Guidance for national tuberculosis and HIV programmes on the management of tuberculosis in HIV-infected children: Recommendations for a public health approach Guidance for national tuberculosis and HIV ... - The Union Consensus statement on the revised World Health Organization recommendations for BCG vaccination in HIV-infected infants. http://www.theunion.org/images/stories/resources/RESS_BCG_Working_Group_Statement_IJTLD_December_2008.pdf
Stop-TB	Guidance for National Tuberculosis Programmes on the management of tuberculosis in children http://www.stoptb.org/wg/dots_expansion/assets/documents/IJTLD_OS_ChildhoodTB_Chapter3.pdf
BCG Atlas	BCG Atlas provides detailed information on current and past BCG policies and practices for over 180 countries. If your country profile needs to be updated please contact Alice Zwerling at alice.zwerling@mail.mcgill.ca or Dr Madhukar Pai at madhukar.pai@mcgill.ca http://www.bcgatlas.org/index.php

Legend: BCG: Bacillus Calmette-Guérin

Table 4. Summary of the World Health Organization policy recommendations on BCG vaccination

	Core Policy Recommendations
1	A single dose of BCG vaccine should be given to all infants as soon as possible after birth in countries with a high burden of tuberculosis
2	Contraindications are infants or persons known to have HIV or other immunosuppressive conditions. In settings with adequate HIV services, BCG vaccination should be delayed for infants born to mothers known to be infected with HIV until these infants are confirmed to be HIV negative
3	BCG revaccination is not recommended as there is little or conflicting evidence of whether this confers additional protection, and revaccination may increase the risk for adverse events.

Legend: BCG: Bacillus Calmette-Guérin; HIV: Human Immunodeficiency Virus

When to stop BCG blanket vaccination

The risk of stopping BCG vaccination in a low-incidence country should be carefully balanced against the risk of an increase in tuberculosis among children. There is no evidence of a threshold incidence; however, International Union Against Tuberculosis and Lung Disease expert opinion suggests less than five in 100 000 new sputum smear positive pulmonary cases as a threshold for stopping herd BCG vaccination [48]. It is noteworthy that even in low-incidence countries, there may be a subset of the population with a higher risk of tuberculosis; therefore, BCG vaccination should be made available to this group [49]. In low-incidence settings, it is advisable to make BCG available for children who are born of parents coming from highincidence countries or who may have lived for prolonged periods in a high-burden country.

Conclusions

In summary, BCG is currently the only available vaccine against tuberculosis. Despite its limitations, it offers reasonable protection against severe forms of tuberculous disease among children. The current policy document offers a rapid guidance on how to procure BCG, plan its use based on the epidemiological situation in the country and manage adverse events (tables 2–4).

This document also represents a further step in the collaboration between the European Respiratory Society (ERS) (and the *European Respiratory Journal (ERJ)*) and WHO on tuberculosis-related activities. Started in 1999 with the development of the ERS tuberculosis guidelines [50] and the publication of the entire series of Wolfheze documents (which helped to modernise the present system of tuberculosis control in Europe) [16], it continued with the publication of two core documents on tuberculosis elimination in Europe [15, 51], guidance on tuberculosis trans-border migration control [52], the ERS/WHO Consilium [4], and a series of important articles on multidrug-resistant tuberculosis [53–55]. In addition, two other important European Centre for Disease Prevention and

Control documents reflecting collaboration with WHO have been published in the *ERJ*, including the European standards for tuberculosis care [56, 57] and the Tuberculosis in Children roadmap documents [58].

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CHAPTER 7

7

Tuberculosis control in prisons: current situation and research gaps

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Abstract

Background: Tuberculosis (TB) in penitentiary services (prisons) is a major challenge to TB control. This review article describes the challenges that prison systems encounter in TB control and provides solutions for the more efficient use of limited resources based on the three pillars of the post-2015 End TB Strategy. This paper also proposes research priorities for TB control in prisons based on current challenges.

Methods: Articles (published up to 2011) included in a recent systematic review on TB control in prisons were further reviewed. In addition, relevant articles in English (published 1990 to May 2014) were identified by searching keywords in PubMed and Google Scholar. Article bibliographies and conference abstracts were also hand-searched.

Results: Despite being a serious cause of morbidity and mortality among incarcerated populations, many prison systems encounter a variety of challenges that hinder TB control. These include, but are not limited to, insufficient laboratory capacity and diagnostic tools, interrupted supply of medicines, weak integration between civilian and prison TB services, inadequate infection control measures, and low policy priority for prison healthcare.

Conclusions: Governmental commitment, partnerships, and sustained financing are needed in order to facilitate improvements in TB control in prisons, which will translate to the wider community.

Key words: Tuberculosis, Prisons, MDR-TB, End TB Strategy, Xpert MTB/RIF, Research

1. Introduction

Tuberculosis (TB) remains a major public health problem, posing specific challenges in numerous geographical areas, particularly in low- and middle-income countries (LMICs) where more than 80% of the global TB burden resides.[1] Additionally, with the current slow (2%) annual decline in TB incidence and the emergence of drug-resistant TB and TB/HIV co-infection, most LMICs will not meet the Millennium Development Goals (MDGs) for TB control by 2015 set by the United Nations.[1] Despite recently gained increased public and political awareness, TB remains a major infectious disease in prison systems, such as in Eastern Europe, for several reasons. These include, but are not limited to, the high prevalence of drug-resistant TB forms, i.e. multi- and extensively drug-resistant TB (M/XDR-TB),[1–14] and intravenous drug use among HIV-infected individuals, which makes prison populations more susceptible to the development of TB.[15]

Prisons are considered reservoirs facilitating *Mycobacterium tuberculosis* (MTB) transmission within their walls, as well as to the community at large. Transmission occurs through prison staff, visitors, and released inmates. The estimated prevalences of latent TB infection (LTBI) and active TB disease in prison systems are reported to be much higher than the average estimates in the general population, irrespective of the economic status and the population TB burden of the country.[16] In European prisons, the prevalence of TB is estimated to be up to 17 times higher than in the general population.[17] A similar epidemiological situation has been described in LMICs, including Bangladesh, Thailand, Ethiopia, and Brazil, where TB prevalence has been reported to be almost four-, eight-, seven-, and 64-times higher, respectively, among prisoners compared to the general population.[18–27] Factors known to contribute to the transmission of MTB strains and that hamper TB control are overcrowding, delayed case detection, poor contact detection, inadequate treatment of infectious cases, high turnover of prisoners, and poor implementation of TB infection control (IC) measures.[28,29] In addition, limited access to timely and quality health care services further exacerbate the situation.

In response to the continuing challenges facing the control of TB and M/XDR-TB, and as the current Global Plan to Stop TB (Stop TB Strategy) 2011–2015 is in its final year, the World Health Organization (WHO) has recently developed the post-2015 End TB Strategy with the goal to end the TB epidemic by 2035.[30] In order to define strategies that efficiently address the End TB Strategy targets, knowledge about solutions for improved TB control in prison systems is needed. In this review, we summarize published knowledge on the challenges of TB control in prison systems and discuss potential solutions, including research priorities for TB control in prisons, in relation to the three pillars of the End TB Strategy.

2. Methods

Articles included in a recently published systematic review on TB control in prison services by Vinkeles Melchers et al.[31] were reviewed; these publications were dated up to June 2011. In addition, relevant articles in English were identified by searching PubMed and Google Scholar, with a temporal range of 1990 to May 2014. Studies were identified using combinations of the search terms "Tuberculosis or TB", "TB Control", "Management", "Public Health", "Prison* or Jail*", and "Prisoner* or Inmate*". Studies in languages other than English and studies published before 1990 were excluded. Articles were also excluded if they described challenges in TB control among populations other than prisoners (e.g., TB contact tracing in the community, health care workers). The selection of articles was based on their public health relevance to TB control in prisons. The references of selected articles were also evaluated to identify additional relevant publications. In addition, conference abstracts of the International Union Against Tuberculosis and Lung Diseases and publications from the WHO over the last 23 years were screened for relevant articles. A total of 637 citations and 332 abstracts were screened, resulting in the inclusion of 96 publications in this review. Because no systematic variables were extracted from the publications included, the challenges and solutions have not been rated on the quality and validity of the evidence.

3. Results and discussion: current evidence

Barriers to tackling TB in prisons are complex and linked strongly to other aspects of both the health and criminal justice systems, and with the cultural, historical, and economic situations of each country. These barriers are summarized in Table 1,[32] and are discussed below in relation to the three pillars of the End TB Strategy.

3.1. Pillar 1: Integrated, patient-centred care and prevention

3.1.1. Universal drug-susceptibility testing and systematic screening of contacts and high-risk groups

The lack of well-equipped laboratory facilities in prisons is well documented.[1,4,20,22,33,34] In addition, a systematic review found that approximately 21% of all studies reporting on TB screening in prisons described the lack of a well-organized health system,[31] potentially leading to the ongoing spread of TB to other prisoners, prison staff, visitors, and to the general population upon release from the prison.[23,35,36] In the absence of adequate diagnostic tools in the prison services, health professionals attempt to use the diagnostic capacity of the civilian sector through national TB programmes (NTPs), such as sputum smear microscopy, chest radiography, and sputum culture.[34] The use of diagnostic services external to the prison system may, however, lead to a delay in diagnosis due to a lack of coordination between the prison and the civilian sector laboratory networks.[17,37,38]

Table 1. Key barriers to tackling tuberculosis in prisons according to the three pillars of the End TB Strategy

Pillar 1: Integrated, patient-centred care and prevention
Lack of laboratory capacities, insufficient quality control and absence of new and improved diagnostic methods
Interrupted supply of quality medicines
Absence of efficient mechanism for direct observation of treatment
Lack of adequate medical facilities
Lack of collaborative TB/HIV activities
Emerging drug resistance
Intravenous drug use among prison populations
Lack of drug substitution and needle exchange programs
Lack of safer sex programs for HIV prevention
Limited social support of vulnerable populations
Limited attention to comorbidities (HIV, hepatitis, psychiatric diseases)
Weak integration between civilian and prison TB services, continuum care of released prisoners
High incarceration rate
Pillar 2: Bold Policies and supportive systems
Low priority that policymakers give to health care (including TB) within the prison system.
Insufficient commitment of prison authorities to address TB prevention, control and care
Unclear responsibilities of different ministries and health authorities
Stewardship of prison health, mismanagement of TB control in penitentiary institutions.
Shortage of qualified and motivated human resources
Shortage of staff training/education and appreciation
Limited or poor patient education
Stigmatization of prisoners with TB
Lack of access to prisons by community representatives, NGOs and organizations with the capacity to support the vulnerable population
Insufficient surveillance, supervision, monitoring and evaluation systems
Inadequate infection control (IC) measures, due to overcrowding and/or organizational and legal challenges in timely separation of patients
Pillar 3: Intensified research and innovation
Lack of funding
Lack of commitment by research institutes
Legal difficulties with research in prison systems

Another main challenge to TB diagnosis is the quality of the bacteriological services. Sputum smear microscopy is not always performed with quality control. Microscopes are poorly maintained, staff may lack quality training in the use of diagnostic tools,[22] and quality assurance including proficiency testing is rarely done.[22,39] The introduction of the GeneXpert MTB/RIF assay is considered an important breakthrough in the fight against TB and multidrug-resistant (MDR-TB). For the first time, a molecular test is simple and robust enough to be introduced outside the conventional or reference laboratory setting,

detecting TB and rifampicin-resistant TB as a proxy for MDR-TB.[40,41] The assay provides results directly from the sputum sample within 2 h and performs well, particularly in sputum smear-positive patients, with an overall sensitivity of 90.4% and specificity of 98.4%.[42] The GeneXpert MTB/RIF assay is suitable for use at the district and sub-district levels, including within the prison system, and should not be restricted to the central/reference laboratory level only.

The current availability of GeneXpert machines in prisons is unclear and this likely differs from country to country. Although testing with GeneXpert MTB/RIF does not require additional laboratory equipment, the sophisticated nature of the device requires care in handling, i.e., a stable and uninterrupted electrical or battery supply to avoid interruption of the procedure and subsequent loss of results, security against theft, adequate storage space for the cartridges, and dedicated staff to perform testing.[40] Addressing this challenge requires general health system strengthening, [5,6,43,44] including the prison sector and especially in LMICs. High-quality laboratory services with up-to-date biosafety measures, [19] updated and renewed detention centres[45] and TB prison hospitals, and continuous training programmes for both staff and prisoners should also be emphasized.[24,34,46]

3.1.2. Ensure equitable access to quality treatment for all people with TB, including drug-resistant TB, and to patient support

Although the Stop TB Strategy entails standardized supervised treatment and uninterrupted pharmaceutical supplies,[47,48] several prisons still encounter challenges in implementing supervised treatment,[38] the uncontrolled circulation and use of suboptimal quality TB drugs,[23,38,46,49] and TB/HIV treatment interactions in prisons with a high co-infection prevalence.[37] Some prisons report that the provision of an effective pharmaceutical supply may be in place, but that prisoners cannot afford treatment as they pay out-of-pocket for health services.[38,49] In addition, there are often other factors affecting treatment adherence in prisons. These may stem from a specific criminal culture among prisoners, the concern of being cured and then referred back to prisons with greater restriction, as well as the hierarchy among prisoners. Approximately 30% of the studies included in a recent systematic review described unsupervised treatment.[31] Therefore, TB control efforts should focus on the provision of effective treatment and/or increasing effectiveness of treatment to TB patients,[22,23,38,50] treatment adherence, and clinical case management.[19,35]

The high turnover of the prison population, between prisons and to the wider community, is a major challenge. This facilitates transmission and consequently the spread of both drug-sensitive and drug-resistant forms of TB.[19,23,51,52] Data from a systematic review identified that 31.2% of studies struggled with effective TB control due to loss to follow-up and a high turnover of prisoners.[31] Consequently, difficulties may be encountered in diagnosing

and treating TB, leading to the further spread of infection to other prisoners, prison staff, and visitors.[23] In addition, approximately 26% of studies in the systematic review reported that TB control in prisons was hampered by a ban on the prisoners attending local clinics or hospitals for 'security reasons'.[31] Within most prison systems, the follow-up of released prisoners is limited or does not occur at all. In Eastern European countries, approximately 60–70% of prisoners are not referred to TB facilities after their release.[53]

3.1.3. Collaborative TB/HIV activities and the management of comorbidities

A core challenge to TB control in prison systems is dealing with the dual epidemics of HIV and TB, as well as other co-infections such as with hepatitis B or C virus. Given the impact that HIV has on TB cases and vice versa, coordination between TB and HIV programmes is vital.[54] However, this may be limited due to poor surveillance of HIV among prisoners with TB,[37] challenges in the diagnosis of TB among people living with HIV,[54,55] a lack of joint planning and mobilization for TB/HIV co-infection, and inadequate human resources capacity for managing TB/HIV.[56,57] In many prisons, the burden of HIV and hepatitis infections among TB patients may be unknown, as periodic surveys or sentinel surveillance are not performed and diagnostic testing and counselling of TB patients is not implemented in all settings.[56,58] Not all TB and HIV/AIDS programmes systematically coordinate plans for the management of dual infections. There is a lack of proper TB/HIV counselling and practice training for counsellors, and of public education and awareness programmes for voluntary HIV testing for individuals, resulting in TB patients not attending HIV clinics. A lack of awareness and education also increases stigmatization among prisoners, and the fear of HIV test results leads to HIV testing being refused.[57] Similar issues are seen for hepatitis and other co-morbidities frequently detected among prisoners. The epidemiological and clinical intertwining of other determinants such as excessive alcohol use or injecting drug abuse and chronic liver disorders (associated with hepatitis B or C virus) with TB places a high burden on the health of prisoners, and also after prisoners are discharged into the community.

Collaborative TB/HIV/hepatitis activities by NTPs and national HIV/AIDS programmes should prioritize prisons, where the prevalence of these infections is high. In addition, a coordinated system, supported by the ministries of health, welfare, and justice or interior, should implement a holistic approach to patients in correctional facilities. Furthermore, preventive activities, including wider health education (e.g. needle exchange or cleansing programmes, or safe sex), should be promoted in order to minimize the harms associated with high-risk behaviours.

3.1.4. Preventive treatment of persons at high risk

Despite the established evidence of the efficacy of isoniazid preventive therapy (IPT) in preventing TB among both HIVinfected and HIV-uninfected individuals, this intervention

has not been fully explored in prisons. A systematic review of published reports showed that only 18 studies were designed to address the intervention in such settings.[59] IPT may effectively interrupt the progression of infection to active TB disease, but questions remain regarding whether IPT should be started in a facility with short imprisonment stays or in settings with high isoniazid resistance, and also which institution should take responsibility for the completion of IPT in the community once the prisoner is released.[19,60]

3.2. Pillar 2: Bold policies and supportive systems

3.2.1. Political commitment with adequate resources for TB care and prevention

Prison health services often have small budgets,[45,60,61] which, in addition to the lack of skilled and motivated manpower,[19,22,38] may jeopardize successful TB control programmes in prisons. Public health attention from donors and other stakeholders towards populations at risk of TB has increased in recent years following the emergence of HIV/AIDS, the more stringent application of human rights principles, health inequalities, and health governance.[62] Nevertheless, there are still challenges in TB control in prisons due to logistical complications, a lack of political commitment, and public indifference towards the prison population, [45] which undermine TB control programme efforts in prison systems.

Improved and strengthened political commitment, including sustainable funding,[38,39,52] is therefore strongly recommended.[31] The significance of ensuring adequate funding for TB control in prison systems is particularly important in Eastern Europe, considering the increased need for MDR-TB diagnostics and treatment. Besides the external funding provided by donors (e.g., Global Fund, US Agency for International Development, International Federation of Red Cross and Red Crescent Societies, the World Bank, and bilateral donors), countries themselves should allocate more local resources in order to gain sustained TB control in prisons.[63] As part of building political commitment, it is essential to ensure that both legislation and national guidelines facilitate TB control in prisons. In particular, the following areas should have a supportive legal basis with minimum standards: (1) guidelines in line with NTPs, (2) a sufficient area per inmate to avoid overcrowding, (3) adequate nutrition, (4) comprehensive IC planning, (5) policies on the release of prisoners with TB and/or their transfer to other facilities, and (6) and integration/collaboration with health care services in the civil sector.[64]

Stewardship of prison health is defined as "all issues concerning governance and responsibility affecting the provision of prison health services of an agreed standard".[65] The question arising here is which ministry should ideally be responsible for the stewardship of health in prisons. This differs by country, and the general health of prisoners may come under the responsibility of the ministry of justice,[66] the ministry of health, or the ministry of internal affairs.[65] The WHO Regional Office for Europe Health in Prison Project (HIPP) provides overall guidance to improve prison health services.[65] Presently, the ministries of

health are in charge of health in prisons in most settings.[65] In other settings, there is a need for close cooperation and collaboration between the ministries of health and the ministries responsible for prisons to plan common activities to improve TB control.

3.2.2. Engagement of communities, civil society organizations, and public and private care providers

Prisoners belong disproportionately to population groups already at high risk of TB (e.g., people who abuse substances, the homeless, migrants from high endemic areas, and other marginalized groups stricken by poverty with little or no access to healthcare), which may partially explain the high prevalence of TB in these settings.[25,28,67] Education and counselling are fundamental to improving patient adherence to treatment. In some settings, community representatives engage inmates in health education and prepare them for treatment follow-up after their release from prison. However, it is clear that prison health services alone may not be able to fully respond to the TB situation in most settings; therefore working in partnership on different levels needs to be encouraged. Prison health services should collaborate closely with other sectors, including civil society and community representatives and health services outside prisons, in order to share diagnostic facilities and improve the referral and support of patients. Prison systems should also partner various ministries on a political level, NGOs, donors, and health experts for improved public awareness and knowledge-sharing.

3.2.3. Infection Control

Many prisons worldwide are overcrowded, well beyond their official capacity.[68] Overcrowded prisons facilitate the spread of mycobacterial strains, as prisoners are in close contact with one another, often for 12 h or more each day without access to fresh air. In some countries, the living conditions of prisoners are poor: spaces in prison cells of less than one square meter per person, bunks stacked three tiers high, and prisoners sleeping in turn, even during daytime hours when they have access to an outside area, or they are kept in isolation cells for long periods without spending time outside at all.[53,68]

Overcrowding, poor ventilation, and prolonged confinement inside cells are all factors conducive to the transmission of airborne infections. Poor ventilation may be due to inadequate prison infrastructure (e.g., lack of windows, no mechanical ventilation), or caused by the prisoners themselves covering the windows to block cold air from entering the room in cold climates, or by hanging clothes on the bars. The lack of mechanical ventilation systems is another major risk factor for contracting TB.[45] Furthermore, many prisoners may be heavy smokers, adding to the unhealthy environment of overcrowded cells.[68]

Overcrowding leading to significantly higher rates of TB transmission in prisons also has implications for rates of TB in the community. Using longitudinal TB and cross-sectional MDR-TB data from 26 Eastern European and Central Asian countries, Stuckler et al.[28] found that each percentage increase in incarceration rate related to an increased TB incidence of 0.34% (population attributable risk, 95% confidence interval 0.10–0.58%, $p < 0.01$), after controlling for several confounders. Conversely, a reduction in custodial sentencing would impact favourably on risk reduction of TB and MDR-TB in the general population.[69]

In light of the challenge of overcrowding associated with increased rates of TB in both the prison and community setting, TB IC is a fundamental element for improved TB control.[70] TB IC is a combination of measures aimed at minimizing the risk of MTB transmission and includes the early and rapid identification of individuals with suspected or known TB, separation of prisoners according to their TB disease type, and effective treatment of infection or disease,[69,71] building design or engineering methods to improve ventilation, disinfecting of the air, and the use of protective measures for staff and visitors in contact with TB patients. TB IC is also a fundamental element of Pillar 2 of the post- 2015 End TB Strategy.[30] A list of IC measures to be conducted in prisons in consideration of these factors is summarized in Table 2.[72]

3.3 Pillar 3: Intensified research and innovation

One of the three main pillars of the End TB Strategy includes research. With the current 2% decline in TB incidence, the MDGs for TB control will not be met by 2015.[73] The need to develop new technologies to accelerate TB control resulted in the launch of the TB Research Movement, with the development of a roadmap for global TB research as its main objective.[73,74] Despite its impact on public health, TB control in prisons has been given a low priority by national health authorities worldwide, particularly in LMICs. This is reflected negatively in the fund allocation, and consequently in research output.[75–77] A recent review of published documents describing TB research priorities showed that 33 documents were published from 1998 to 2010 describing the importance of research on new medicines and diagnostics.[78] None of the documents retrieved directly addressed TB research in prisons.

Table 2. Summary of infection control measures to be conducted in prisons

Preventing spread of infection from community to prison by using intensified TB screening for new or transferred prisoners and preparing special blocks "Quarantine" or cells (to be used for 1-2 weeks) for new or transferred prisoners.
Preventing TB infection among prisoners (transmission from one TB prisoner to other prisoners) or to prison's staff by conducting a contact investigation for TB suspects and cases, improving infection control (e.g. implementing organizational, administrative, and environmental interventions) in prisons and using IC for prisoners.
Preventing infection of family members and the community by a released prisoners or prison staff by examining prisoners before release and examining prison staff regularly.
Isolation measures for TB cases and/or suspects when patients are screening or diagnosed within the prison system.

Table 3. Priorities for research related to TB control in prisons.

Epidemiological research
Actual burden of tuberculosis (drug susceptible and resistant strains) and TB/HIV in prisons worldwide
Best tools to measure the TB burden
Social determinants of TB infection and transmission inside prisons
Prevalence of LTBI in high-burden-countries
Impact of scaling-up current preventive regimens on TB prevalence in prisons
Contribution of TB in prison to TB transmission in the community (attributable risk)
Operational (health services) research
Best operational model to enhance case-finding and its impact on mortality and transmission in prisons
Definition of optimal algorithms for diagnosis of all forms of active TB and best model to rule out TB among high risk group (particularly HIV-infected)
Barriers of achieving treatment adherence and strategies to improve treatment management particularly after prisoners' release after short detention
Impact of individual infection control methods and proper cost-effective methods of its implementation
Cost-effectiveness studies of the scaling-up of TB/HIV and MDR-TB services in prisons
Best model to integrate TB/HIV/STD services
Proper reporting and recoding system suitable for prisons
Diagnostics
New, point of care, same-day diagnostic tool to diagnose active TB
Rapid tests for diagnosing drug-resistant TB
Feasibility, impact and cost-effectiveness of new automated nucleic acid amplification test (e.g. GeneXpert) for use in prisons of remote and/or resource-limited settings, particularly for new arrival screening
Optimal and cost-effective modelling of diagnosing LTBI and active TB
Developing a proper diagnostic tool to differentiate between LTBI and active TB, particularly among HIV-infected prisoners
Treatment
Newer and safer TB medications to combat the growing epidemic of TB and M/XDR-TB in prisons
Shorter treatment regimens to treat LTBI and active TB
Effectiveness and safety of currently available LTBI treatment regimens in correctional settings vis a vis the high prevalence of blood-borne co-infections (i.e. HIV, Hepatitis C, Hepatitis B)
Safety, efficacy and cost-effectiveness of new shorter LTBI regimens (e.g. combination of isoniazid and rifapentine once weekly for 12 weeks)
Optimal time to start ARV and exploration of possible drug-drug interactions with newer TB medications

TB, tuberculosis; LTBI, latent tuberculosis infection; MDR, multidrug-resistant; STD, sexually transmitted disease; M/XDR-TB, multi- and extensively drug-resistant TB; HCV, hepatitis C virus; HBV, hepatitis B virus; ARV, antiretroviral.

In order to better allocate economic and human resources, it is important to adequately estimate the burden of disease and the risk of developing TB in prison.[79] Given the

difference in dynamics and population, guidelines outlining TB research priorities need to be developed specifically for correctional institutions.[76] The areas for research to be addressed in relation to prisons, as listed in Table 3, are of high priority.[74,75,78] There are still concerns about conducting studies among vulnerable populations, including prisoners, and ethical considerations related to prisoners need to be addressed properly when conducting research in these settings.

4. Conclusions

Currently, a complex range of activities is required to tackle the alarming situation of TB, M/XDR-TB, and TB/HIV control in prisons. The requirements for enhanced TB control in prisons are good governance, clear strategies to diagnose and treat TB patients, adherence to internationally established IC policies, and the performance of cost-effectiveness analyses to evaluate screening procedures and other control strategies. Released prisoners with active TB disease need to be followed-up by health authorities in the civilian sector and NTP-based local health centres, or organizations collaborating with NTPs. To minimize the interruption of treatment for released prisoners, implementation of the following interventions is recommended: (1) discharge or referral planning, (2) post-release follow-up, and (3) notification of unplanned releases and monitoring of referrals. If NTPs or ministries of health are responsible for TB control in the prison system, the establishment of follow-up mechanisms is probably more likely to occur, and gaps between public health and prisons are less likely to exist.

In addition, it is crucial to prepare effective plans for human resource development covering entire processes, such as basic education (in- and pre-service), retraining, on-the-job training, supervision, career development, salary scales, job descriptions, and enhanced IC measures. Although the Directly Observed Treatment Short-course (DOTS) has been declared the most cost-effective health strategy available by the World Bank, there is still work to be done to improve general TB management among prisoners. It is argued that if there is a failure to implement TB control successfully in prisons, it will affect prison and public health services dramatically in the near future, due to increased numbers of cases within the prison services and community, as well as higher numbers of M/ XDR-TB and/or TB/HIV cases. New tools, such as the GeneXpert MTB/RIF, should be implemented in central prison hospitals, or facilities where prisoners receive TB treatment.

Although we are entering an exciting period of innovation, e.g. introduction of GeneXpert MTB/RIF and new medicines like delamanid and bedaquiline,[41,80,81] TB control in prisons remains a neglected priority. In addition, the increased cost of new drugs (USD 900 and USD 3000 for bedaquiline in LMICs and high-income countries, respectively, for a 6-month course)[82] and the resources needed for pharmacovigilance and the management of side effects, remain a barrier to utilization, particularly in the prison sector where resources

are even more limited. No real improvement can be facilitated without clear commitment from national governments and partnerships and sustained financing, in line with the End TB Strategy. In order to achieve this, the principle "good prison health is good public health"[83] needs to be fully recognized.

Conflict of interest

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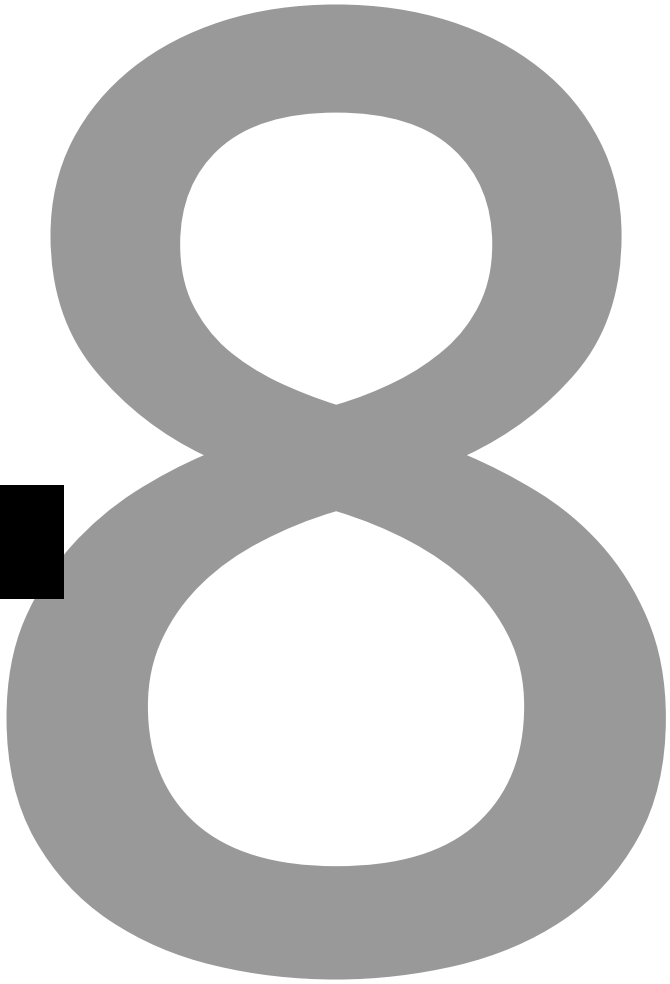
CHAPTER 8



A new roadmap for childhood tuberculosis

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On Oct 1, 2013, WHO and global partners launched a roadmap to end tuberculosis deaths in children worldwide.[1] The roadmap identifi es key actions that must be taken, including increased and targeted research, partnerships between key stakeholders, and strategic economic investment. The roadmap also shows the crucial lack of global emphasis on tuberculosis prevention and treatment for one of the most vulnerable populations. This intervention comes at a pivotal juncture because rates of drugresistant tuberculosis have been increasing worldwide, particularly in the WHO European Region, with severe implications for child tuberculosis morbidity and mortality.

Globally, children younger than 15 years account for about 6% of the 8·6 million cases of tuberculosis, and about 5% of the 1·4 million deaths that occur annually from the disease.[2,3] Children have been traditionally viewed to pose less of a risk for transmission than adults because they often have paucibacillary disease, which is also harder to diagnose with sputum smear microscopy, culture, and molecular tests.[4] If tuberculosis is undetected and untreated, children are at high risk of death, especially in the context of multidrugresistant and extensively drug-resistant tuberculosis. 15 of the 27 countries with a high burden of multidrugresistant and extensively drug-resistant tuberculosis worldwide are in the WHO European Region,[2] with 99% of the regional disease burden in 18 high-priority countries (Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Moldova, Romania, Russia, Tajikistan, Turkey, Turkmenistan, Ukraine, and Uzbekistan).[5] 6% of the total estimated incidence of new and relapsed tuberculosis cases occurred in these countries (376 200 cases),[2,5] in 2011, an estimated 23 000 children had tuberculosis, of whom nearly 5000 are estimated to have had multidrug-resistant or extensively drug-resistant disease. These estimates contrast sharply with the fewer than 1000 cases of childhood tuberculosis that were detected and reported in these countries.[2,5]

In response to the alarming increase in multidrugresistant and extensively drug-resistant tuberculosis in the WHO European Region, in 2011 the Consolidated Action Plan to Prevent and Combat Multidrug and Extensively Drug Resistant Tuberculosis (2011–15) was endorsed by the sixty-fi rst Regional Committee for Europe, and implemented in all 53 member states.6,7 The plan includes essential milestones and activities for childhood tuberculosis, with the aim to scale-up access to treatment; prioritise childhood tuberculosis in member states' national strategic plans; and develop a special response for diagnosis and treatment of tuberculosis in children, including identifying policies (or lack of policies) that contribute to underdiagnosis.

The table summarises data on national childhood tuberculosis policies collected by the WHO Europe task force for childhood tuberculosis from 15 (of the 18) high-priority countries that provided policy information from September, 2012, to January, 2013.[3]

At present, the 15 countries have policies that adhere to the 2006 WHO guidelines for childhood tuberculosis[4] with regard to contact-tracing of close household contacts, detection with tuberculin skin testing, and provision of isoniazid preventive treatment for children with a close household tuberculosis contact. However, only eight countries have policies for contact tracing for children with a close non-household contact (as recommended by WHO for children younger than 5 years[8]). Additionally, four countries recommend a multidrug-resistant tuberculosis treatment regimen only in children with bacteriologically confirmed multidrug-resistant tuberculosis. However, since bacteriological confi rmation is often diffi cult in children, WHO recommends that, if active tuberculosis disease develops in children with a close contact with multidrug-resistant tuberculosis, a multidrug-resistant tuberculosis drug regimen should be promptly started. Although 11 countries have this policy in place, its efficacy is predicated on eff ective contact investigation. For children who are detected with active tuberculosis or are given preventive therapy for latent infection, several countries require hospital admission for either the initial 2 month phase or the entire length of preventive and active tuberculosis treatment (three and seven countries, respectively). However, admission of children to tuberculosis wards for an unnecessarily long duration places them at high risk of primary infection or reinfection with multidrug-resistant or extensively drug-resistant tuberculosis.[9,10] Forthcoming updated WHO guidelines for the management of childhood tuberculosis will add clarity for countries about these and other issues, including detection with molecular diagnostics and use of paediatric drug formulations.

In the context of multidrug-resistant and extensively drug-resistant tuberculosis, a priority in the WHO European region is to accelerate the adoption of updated childhood tuberculosis guidelines into national strategic tuberculosis policies. Additionally, eff orts to ensure that policy is aligned with practice remain at the core of eff ectively detecting disease and saving lives of children with tuberculosis. In high-priority countries, there is a crucial scarcity of qualifi ed human resources to manage childhood tuberculosis and multidrugresistant and extensively drug-resistant tuberculosis, and irregular access to second-line drugs is still a challenge. The new roadmap for childhood tuberculosis importantly serves as a call to action for all stakeholders in child health to urgently address these issues.

Key actions to increase awareness and capacity for contact investigation, management of childhood tuberculosis, and surveillance are in line with the Consolidated Action Plan. These actions will be vital to shift policy and place a spotlight on prevention and combat of multidrug-resistant and extensively drugresistant tuberculosis in the most vulnerable populations.[4]

We declare that we have no conflicts of interest. Collection of policy data by the WHO Regional Office for Europe, Childhood TB taskforce was funded by the USAID Regional Platform. Analysis of the data was supported through the SORT IT operational research programme run by the Operational Research Unit (LUXOR), Médecins sans frontières (Brussels and Luxembourg), The Centre for Operational Research, International Union against TB and Lung Disease (France), The Union South-East Asia Regional Office, and the Special Programme for Tropical Disease Research (TDR) at the WHO (Geneva). The views expressed in this Comment are solely those of the authors.

Table 1. Detection, Preventive- and Active- TB Treatment Policies for Children

	Number of high-priority countries (n=15)*
Case detection	
Contact tracing†	
Close household	15
Close non-household	8
Casual	7
Community	6
Examinations if tuberculosis contact†	
TST	15
Bacteriological examination	9
Interferon-γ-release assays	3
Radiograph of the chest	14
Fluorography	3
CT	9
Other blood analyses	10
Preventive treatment	
Preventive treatment for latent tuberculosis†	
Children with tuberculosis contact, irrespective of age and irrespective of TST results	7
Children with tuberculosis contact, irrespective of age with a positive TST	8
Children with tuberculosis contact, with positive TST of certain age range	2
Children detected through mass tuberculin skin testing with a positive TST, irrespective of age	2
Children with HIV	8
Other	7
Type of preventive treatment†	
Isoniazid	15
Other	4
Preventive treatment for child contacts of MDR tuberculosis patients (individualised treatment on the basis of drug-resistance pattern of index case)	4
Preventive admission to hospital	
Yes, for the entire treatment period	3
Yes, for the initial period	3
No, treatment is given ambulatory for the full period	6
Ambulatory for the full period with a proportion of children referred to sanatoriums	3
Treatment for active tuberculosis disease	
Paediatric national guidelines	14
Standardised treatment for active or assumed drug-sensitive tuberculosis	15
Children prescribed MDR regimen	
Only children with bacteriologically confirmed MDR tuberculosis	4
Both children with bacteriologically confirmed MDR tuberculosis and children with active tuberculosis in close contact with patients with infectious MDR tuberculosis	11
Type of MDR treatment	
Individualised	9
Standardised	3
Both	2
Admission to hospital for active tuberculosis†	
Yes, for the entire treatment period	7
Yes, for the initial period	3
No, ambulatory for the full period	5
Ambulatory treatment preferred, but hospital stay might be necessary	5

TST=tuberculin skin test. MDR=multidrug-resistant. *Armenia, Belarus, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Moldova, Russia, Tajikistan, Turkey, Turkmenistan, Ukraine, and Uzbekistan. †Categories not mutually exclusive.

Table: **Number of countries with policies for detection, preventive treatment, and active treatment of children with tuberculosis**

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CHAPTER 9

9

Tuberculosis care among refugees arriving in Europe: a ERS/WHO Europe Region survey of current practices

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Abstract

No evidence exists on tuberculosis (TB) and latent TB infection (LTBI) management policies among refugees in European countries.

A questionnaire investigating screening and management practices among refugees was sent to 38 national TB programme representatives of low and intermediate TB incidence European countries/ territories of the WHO European Region.

Out of 36 responding countries, 31 (86.1%) reported screening for active TB, 19 for LTBI, and eight (22.2%) reporting outcomes of LTBI treatment. Screening for TB is based on algorithms including different combinations of symptom-based questionnaires, bacteriology and chest radiography and LTBI screening on different combinations of tuberculin skin test and interferon-γ release assays. In 22 (61.1%) countries, TB and LTBI screening are performed in refugee centres. In 22 (61.1%) countries, TB services are organised in collaboration with the private sector. 27 (75%) countries answered that screening for TB is performed as per national and international guidelines, while 19 (52.7%) gave the same answer with regards to LTBI screening. Infection control measures are inadequate in several of the countries surveyed.

There is need for improved coordination of TB screening in Europe to implement the End TB Strategy and achieve TB elimination.

Introduction

According to the most recent World Health Organization (WHO) Global TB Report the estimated annual tuberculosis (TB) incidence decreased globally by an average of 1.5% per year since 2000 and the estimated TB prevalence in 2014 was 42% lower than in 1990 [1]. However, an estimated 9.6 million people worldwide developed active TB in 2014, among them, 12% had HIV infection [1]. During the same year, TB caused 1.5 million deaths, making it one of the most common causes of death from an infectious disease alongside HIV.

In 2014, a total of 329 270 TB cases were reported from 51 countries in the WHO European Region (notification rate: 36.7 cases per 100000 population), with 33 000 estimated deaths [2]. The estimated incidence in Europe represents 3% of the global TB burden.

TB is considered a major public health challenge in many countries worldwide, particularly among vulnerable populations, such as individuals at higher risk of exposure to discrimination, hostility or economic adversity. These factors unfortunately afflict the lives of many migrants and refugees (here defined in agreement with the 1951 "Convention and Protocol relating to the status of Refugees": www.unhcr.org/3b66c2aa10.html) [1–5].

Several factors have contributed to increase population mobility in the WHO European Region, such as the establishment of the European Union (EU) and free movement within the Newly Independent States (NIS), particularly for seasonal labour [5, 6], although refugees' problems are specific. This increased population mobility poses challenges for TB control and requires effective and sustainable mechanisms to ensure quality TB and latent TB infection (LTBI) prevention, diagnosis and treatment [5, 7].

The need for coordinated intervention in these areas is justified from the perspective of individual human rights (independent of legal or residential status of the subject) as well as public health pre-requisites to control and ultimately eliminate TB, including multi- and -extensively drug resistant TB (MDR-TB and XDR-TB) [3, 8–10].

For refugees, full access to TB diagnosis and treatment (with guarantee of protection from deportation until the end of treatment) has been recommended by WHO; this is in the interest of both the individual and the wider hosting community in terms of TB control and elimination [11–15]. In 2015, more than one million migrants and refugees reached Europe by land and sea. In 2014 the estimated figure was significantly lower (219 000) [4, 16]. According to official data, an estimated 181 673 new refugees and migrants arrived in Europe between January 1 and April 26, 2016, with 1261 reported deaths. 82% of arrivals via the Mediterranean sea originated from 10 countries only [16]. At the current time, the four countries from which most refugees originate are the Syrian Arab Republic (43% of

the overall flow), Afghanistan (23%), Iraq (14%), Pakistan (4%) and Iran (4%) (see also: https://ec.europa.eu/eurostat/statistics-explained/index.php/Asylum_statistics).

Despite the recent release of resolutions and statements by bodies such as WHO, the European Respiratory Society (ERS) and the EU [4, 17], not much is known about the policies in force in European countries with regards to TB and LTBI management among refugees upon arrival.

In light of the ongoing refugee situation in Europe, the aim of this ERS/WHO European Region study (performed through the ERS ad hoc Working Group on TB Advocacy) is to document the policies and practices of low and intermediate TB incidence European countries with regards to detection and management of TB and LTBI among refugees.

Methods

Survey questionnaire

In September–October 2015, experts from the ERS, WHO Regional Office for Europe and the WHO Collaborating Centre in Tradate, Italy, as members of the ERS ad hoc Working Group on TB Advocacy, (www.ersnet.org/index.php?option=com_flexicontent&view=items&id=5200-tb-advocacy-working-group.html) developed a short questionnaire for a rapid survey containing multiple choice and open-ended questions on screening and management of TB and LTBI among refugees in Europe. The questionnaire was finalised after reviewing suggestions and comments received from the members of the ERS TB Advocacy ad hoc Working Group and reaching overall consensus among the members. In addition to basic demographic data of the respondents, the survey comprised questions on the following subject areas: screening for and management of TB/LTBI; guidelines, legislation and evidence for current practice; cross-border TB care; and organisational aspects of TB care and infection control measures.

The questionnaire was sent to the national TB programme representatives of all EU/European Economic Area countries of the WHO European Region, Switzerland and six other countries who have hosted, or were deemed likely to host, or become a transient country for a significant number of refugees in the near future. The six additional countries were the current EU candidate countries (Albania, Bosnia and Herzegovina, the former Yugoslav Republic of Macedonia, Montenegro, Serbia and Turkey). The survey, along with a cover letter for additional information, was sent to each of the national TB programme representatives on October 23, 2015, with an initial deadline set for November 6, 2015. Furthermore, there was an offer for the TB programme representatives to conduct a telephone interview to complete the survey, should returning the document prove too difficult by the deadline provided. On November 9, 2015, a reminder email was sent to

programme representatives who had not responded. The survey was closed on February 24, 2016.

Data analysis

The results of the survey were entered into a Microsoft Excel programme (Excel 2010; Microsoft Corporation, Albuquerque, NM, USA) and double-checked (L. D'Ambrosio; R. Centis) prior to analysis. Results produced a mixture of quantitative and qualitative data, with descriptive statistics being calculated where appropriate, and supplemented with qualitative information provided by responders to the survey.

Ethics

As a broad evaluation of current policies and practices within countries, ethical approval was not required because the study did not collect individualised information on subjects.

Results

36 (94.7%) out of 38 countries contacted responded to the questionnaire. The results from section 1 (Screening for TB and LTBI among refugees in the European Region) are summarised in table 1.

Refugees are routinely screened for active TB by the majority of the countries (31 (86.1%) out of 36), with the exception of Italy, Monaco and Portugal where a non-systematic screening is performed (only in symptomatic individuals); no screening is performed in Former Yugoslavia Republic of Macedonia (length of stay in holding centre is not long enough for screening to take place) and Serbia (insufficient governmental funding). 19 (52.7%) countries (Belgium, Bulgaria, Croatia, Cyprus, Estonia, France, Greece, Iceland, Lithuania, Luxembourg, Malta, Montenegro, Norway, Romania, Slovakia, Spain, Sweden, Turkey and the UK) screen systematically for LTBI among refugees, eight (22.2%) countries (Denmark, Finland, Germany, Italy, Monaco, the Netherlands, Portugal and Slovenia (which reported low numbers)) do not perform it systematically and nine (25%) do not screen at all for LTBI (Albania, Austria, Czech Republic, Hungary, Ireland, Latvia, Former Yugoslav Republic of Macedonia, Serbia and Switzerland) (figure 1).

However, almost half of the countries (8 (47%) out of 17) that currently do not screen for TB and LTBI have plans to introduce it for TB and/or LTBI in the near future. There is a legal obligation to screen for TB and/or LTBI in 21 (58.3%) of the 36 countries responding to this survey.

Screening for TB is performed with algorithms using different combinations of symptom-based questionnaires (21 (58.3%) out of 36, of which one not systematically collected), bacteriology (18 (50%) out of 36, sputum smear/culture collection of which nine for

symptomatic individuals only) and chest radiography (27 (75%) out of 36, of which two do not perform systematically, while in Germany, TB screening of adult immigrants (⩾15 years old) is almost systematically performed by chest radiography (with exception of pregnant ladies as per legal act)); five countries (Denmark, Italy, Monaco, Portugal and Turkey) do not systematically perform any TB-specific examination. In two countries (Croatia and Hungary), routine bacteriology for TB (sputum smear and culture) is part of the screening procedure.

Similar to the findings described by a previous ERS/WHO Europe Region Study [10], LTBI screening is performed by using different combinations of tuberculin skin test (TST) and interferon-γ release assays (IGRAs) in 23 (63.8%) out of 36 different European countries (eight (22.2%) out of 36, TST only, 11 (30.5%) out of 36, TST plus IGRA, four (11.1%) out of 36, TST plus IGRA in selected cases (only in Bacillus Calmette–Guérin non-vaccinated children aged <12 years and after TB exposure in the Netherlands; and in case of recent exposure to TB in Portugal, Slovenia and Monaco).

Table 1. Questionnaire Section I: Screening for TB and LTBI among refugees in Europe

Active TB screening Yes/No	**LTBI screening Yes/No**	**Plans to implement screening for active TB / LTBI Yes/No**	**Legal requirement for screening Yes/No**	**Active TB screening performed by: - Symptomatic questionnaire - Sputum collection - Chest radiography - Other**	**Routinely sputum collection for microbiological study/culture/ Xpert Yes/No**	**LTBI screening performed by: - TST - IGRA - Other**	**Place of screening: - Pre-arrival - On arrival - In refugees centres - In the community - Other**	**Information on TB rates in the country of origin to decide for the screening process Yes/No**	**Screenings Number 1,2…**
Yes 31/36 (86.1%)	Yes 19/36 (52.7%)	Yes 8/17* (47%)	Yes 21/36 (58.3%)	Yes systematic symptoms-based questionnaires 20/36 (55.5%) Yes not systematic symptoms-based questionnaire 1/36 (2.7%) Yes systematic bacteriology 9/36 (25%) Yes bacteriology for symptomatic individuals only 9/36 (25%) Yes systematic chest radiography 25/36 (69.4%)+ Yes not systematic chest radiography 2/36 (5.5%)	Yes 2/36 (5.5%)	Yes TST 19/36 (52.7%) Yes TST only 8/36 (22.2%) Yes TST plus IGRA 11/36 (30.5%) Yes not systematic TST plus IGRA 4/36 (11.1%)	Refugees centres only 10/36 (27.7%) On arrival only 4/36 (11.1%) In the community only 1/36 (2.7%) In the National TB Programme Centre only 1/36 (2.7%) On arrival and in refugees centres 6/36 (16.6%) On arrival and at pre-arrival 1/36 (2.7%) On arrival and in the community 1/36 (2.7%) On pre-arrival and in the community 1/36 (2.7%) In refugees centres and in the community 6/36 (16.6%) Not applicable information 5/36 (13.8%)	Yes 14/36 (38.8%)	Only once 28/31# (90.3%) More than once 3/31# (9.7%)

No 2/36 (5.2%)	No 9/36 (25%)	No 5/17* (29.4%)	No 12/36 (33.3%)	Other procedures § 1/36 (2.7%)	No 34/36 (94.4%)	Not applicable (for both) 13/36 (36.1%)		No 19/36 (52.7%)	
Not sistematically 3/36 (8.3%)	Not sistematically 8/36 (22.2%)	Not answered 3/17* (17,6%)	Not applicable 3/36 (13.8%)	Not systematic screening for active TB 5/36 (13.9%)**				Not applicable 3/36 (13.8%)	
		Not applicable 1/17* (5.9%)							

Footnotes: TB: tuberculosis; LTBI: latent Tuberculosis infection; TST: tuberculin skin test; IGRA: Interferon-Gamma Release Assays; *denominator is the number of countries that do not (or do not systematically) screen for TB/LTBI; +: in Germany, TB screening almost systematically performed by CXR for adult immigrants (≥ 15 years-old) §: initial algorithm with tuberculin skin tests (TST) and blood examination; #: denominator is the number of countries that screen for TB/LTBI; **: numerator includes countries which do not systematically perform any examination

In 22 (61.1%) out of 36 countries, TB and LTBI screening are performed in refugee centres, using also other combinations of measures (See table 1 for details). The decision to perform TB/LTBI screening is determined by the TB incidence rate in the country of origin of refugees in 14 (38.8%) out of 36 of the surveyed countries. No single threshold was provided. In the majority of countries where any screening takes place, it is performed only once (28 (90.3%) out of 31). The results from section 2 (Management of TB and LTBI among refugees in Europe) are summarised in table 2.

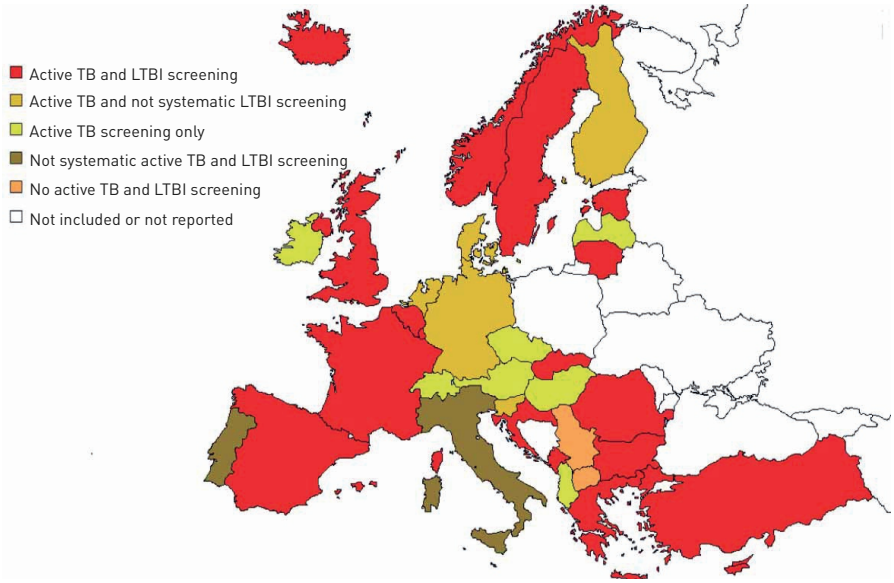

Figure 1. Summary of the countries screening for tuberculosis (TB) and latent TB infection (LTBI).

In the majority of countries (24 (66.6%) out of 36) treatment after diagnosis of active TB in a refugee is required, whereas in Denmark, Monaco, the Netherlands and Portugal, TB treatment is voluntary; in six other countries (Belgium, Germany, Ireland, Sweden, Switzerland and the UK) individuals cannot be legally forced to take medications, but can usually be convinced to start anti-TB treatment; involuntary isolation is foreseen in case of refusal to comply with treatment, while in Serbia isolation is only considered for MDR-TB patients who refuse treatment and, in Macedonia, no TB treatment is proposed due to the short length of stay in the country. Overall, no EU country reported that TB detection was a reason for deportation.

Anti-TB treatment is proposed immediately after diagnosis in the majority of countries (26 (72.2%) out of 36), where costs are covered by central governmental funds (26 (72.2%) out of 36). Almost three-quarters (23 (63.8%) out of 36) report that efforts are ongoing to adapt TB services to refugees' specific needs through specific national/regional programmes and

improved cooperation with the non-governmental sector. A similar number of countries (22 (61.1%) out of 36), directly or indirectly (through certified non-governmental organisations (NGOs)) allow refugees access to TB services. Among countries with general or specific regional/national programmes (or guidelines) for TB management in refugees (14 (38.8%) out of 36), more than half (nine (64.2%) out of 14) report difficulties in fully complying with requirements of their own guidelines, given the high number of refugees in the present situation. Further details on specific national programmes are available in table 2.

The results from section 3 (Guidelines, Legislation and Evidence on the results of screening and treatment of TB and LTBI in Europe) are summarised in table 3. In particular, 27 (75%) 36 countries answered that screening for TB is done as per national and international guidelines (offering the same services to refugees and nationals), while 19 (52.7%) out of 36 gave the same answer with regards to LTBI screening. Similarly, while 22 (61.1%) out of 36 countries confirmed that they collect data on the yield of active TB screening among refugees (with Estonia, Finland, Norway and the UK partially/not systematically collecting data), only 11 (30.5%) out of 36 countries (Bulgaria, Finland, France, Iceland, Italy, Lithuania, Norway, Slovakia, Slovenia, Turkey and the UK) are equipped to collect similar data for LTBI screening (Finland, Norway and the UK providing data not systematically). Finally, detailed information on TB treatment outcomes is available in 19 (52.7%) out of 36 countries, while treatment completion rates for LTBI therapy among refugees are available in only eight (22.2%) countries (Bulgaria, France, Iceland, Netherlands, Portugal, Slovakia and Slovenia and Turkey).

The results from section 4 (Organisational aspects of TB care and infection control issues) are summarised in table 4. Seven (19.4%) countries (Austria, Croatia, Germany, Greece, the Former Yugoslavia Republic of Macedonia, Serbia and Turkey) reported to host >250000 refugees in the 6 months preceding the survey, Hungary notified a range between 100 001 and 250 000, while Italy and Sweden reported hosting between 50 001 and 100 000 refugees. In the vast majority of the countries (30 (83.3%) out of 36), public sector services are in charge of managing refugees for TB-related issues, complemented by international organisations (*e.g.* Red Cross in Bulgaria, Denmark, the Former Yugoslavia Republic of Macedonia, Serbia and Spain; the International Organization for Migration in Romania and Medicine du Monde in the UK).

Several problems were reported among the different countries, including internal and external communication and coordination issues, cultural mediation/language differences and inadequate funding or human resources. The sheer volume of refugees was also cited as a challenge in eight (22.2%) countries (Austria, Belgium, Germany, Greece, Italy, the Netherlands, Norway, Serbia). Although respirators are generally available to protect staff and complement administrative infection control measures, a general lack of consistency with international guidelines emerged from the countries' answers.

Table 2. Questionnaire Section II: Management of TB and LTBI among refugees in Europe

Procedures if active TB is diagnosed: **- Refusal of asylum** **- Obligation to undergo treatment** **-Other**	**Obligation to undergo treatment:** **a. Where** **b. When** **c. Funding**	**Procedures if LTBI is diagnosed:** **- Refusal of asylum** **- Obligation to undergo preventive therapy** **-Other**	**Obligation to undergo preventive therapy:** **a. proposed to all positive for LTBI** **b. same procedure as native nationals positive for LTBI** **c. therapy delivery** **d. funding**	**Regional/ national specific programmes for TB management in refugees Yes/N o**	**Regional/ national programmes to provide sensitive services Yes/No**	**Special measures to deal with undocumented migrants Yes/No**	**Discrepancy/ ies between guidelines and implementation Yes/No**	**TB Management funding**
No Refusal of asylum 34/36 (94.4%) Yes Obligation to undergo treatment 24/36 (66.6%) Other 10/36 (27.7%) Not applicable 2/36 (5.5%)	**a.** Treatment in Hospital 24/36 (66.6%) Not applicable 8/36 (22.2%) Not answered 4/36 (11.1%) **b.** Treatment immediately started after diagnosis 26/36 (72.2%) Not answered 2/36 (5.5%) Not applicable 8/36 (22.2%) **c.** Governmental funds 26/36 (72.2%) Not answered 2/36 (5.5%) Not applicable 8/36 (22.2%)	No Refusal of asylum 20/36 (55.5%) Yes Obligation to undergo preventive therapy 8/36 (22.2%) Other 18/36 (50%) Not applicable 8/36 (22.2%)	**a.** Proposed to all positive for LTBI 3/36 (8.3%) No, proposed for specific groups and ages only 7/36 (19.4%) Not applicable 24/36 (66.6%) Not answered 1/36 (2.7%) **b.** Same procedure as native nationals positive for LTBI 7/36(19.4%) Not applicable 24/36(66.6%) Not answered 5/36 (13.8%) **c.** Therapy delivered at Chest/DOT/TB centres/ TB specialists 7/36 (19.4%) Not applicable 23/36(63.8%) Not answered 6/36 (16.6%)	Yes 10/36 (27.7%) No, not fully specific 4/36 11.1%) No 22/36(61.1%)	Yes 23/36(63.8%) No 1/36 (2.7%) Not answered 12/36 (33.3%)	Yes 22/36 (61.1%) No 1/36 (2.7%) Not answered 13/36 (36.1%)	Yes 9/36 (25%) No 6/36 (16.6%) Not answered 8/36 (22.2%) Not applicable 13/36 (36.1%)	Government funds 22/36 (61.1%) Not answered 12/36 (33.3%) Not applicable 2/36 (5.5%)

			d. Government budget 9/36 (25%) Not applicable 23/36 (63.8%) Not answered 4/36 (11.1%)					

Footnotes: TB: tuberculosis; LTBI: latent Tuberculosis infection; DOT: direct observed therapy

Table 3. Questionnaire Section III: Guidelines, Legislation and Evidence on the results of screening and treatment of TB and LTBI in Europe

Screening and management of active TB among refugees according to national or international guidelines/ legislation in force Yes/No	**Screening and management of LTBI among refugees according to national or international guidelines/ legislation in force Yes/No**	**Data collection in place to assess the yield of screening for active TB among refugees Yes/No**	**Data collection in place to assess the yield of screening for LTBI among refugees Yes/No**	**Data collection in place to assess treatment success rates of active TB among refugees Yes/No**	**Data collection in place to assess completion rates of LTBI among refugees Yes/No**
Yes 27/36 (75%)	Yes 19/36 (52.7%)	Yes 18/36 (50%)	Yes 8/36 (22.2%)	Yes 19/36 (52.7%)	Yes 8/36 (22.2%)
No 3/36 (8.3%)	No 7/36 (19.4%)	Yes partially or not systematically 4/36 (11.1%)	Yes partially or not systematically 3/36 (8.3%)	No 10/36 (27.7%)	No 20/36 (55.5%)
Not applicable 1/36(2.7%) Not answered 5/36 (13.8%)	Not applicable 5/36 (13.8%) Not answered 5/36 (13.8%)	No 8/36 (22.2%) Not answered 4/36 (11.1%) Not applicable 2/36 (5.5%)	No 18/36 (50%) Not answered 4/36 (11.1%) Not applicable 3/36 (8.3%)	Not answered 6/36 (16.6%) Not applicable 1/36 (2.7%)	Not answered 6/36 (16.6%) Not applicable 2/36 (5.5%)

Footnotes: TB: tuberculosis; LTBI: latent Tuberculosis infection

Table 4. Questionnaire Section IV: Organisational aspects of TB care and infection control issues

N. of refugees hosted at the national level during the last 6 months **- <50,000** **- 50,001 – 100,000** **- 100,001 – 250,000** **- >250,000**	**Organisation(s) responsible for first-line medical care of refugees at the national level**	**Special measures for cross-border care when a refugee is diagnosed active TB** **Yes/No**	**Priority problems identified at the national level to manage TB among refugees**	**Personal protection/ infection control measures in place for presumptive active TB cases** **- No specific measures in place** **- Respirators used for staff in contact with refugees** **- Respirators used for staff and surgical masks for individuals with possible TB or other respiratory disease** **- Other**
<50,000 25/36 (69.4%) 50,001 – 100,000 2/36 (5.5%) 100,001 – 250,000 1/36 (2.7%) >250,000 7/36 (19.4%) Not answered 1/36 (2.7%)	National and/or local medical/ public health services (including Ministry of Health) 21/36 (58.3%) Medical staff of holding centres 3/36 (8.3%) Primary health care clinics 3/36 (8.3%) Federal /State Agencies for Refugees 3/36 (8.3%) Red Cross/International Organizations 6/36 (16.6%) Public/private providers 1/36 (2.7%)	Yes 17/36 (47.2%) No 14/36 (38.8%) Not answered 3/36 (8.3%) Not applicable 2/36 (5.5%)	System in place overloaded by the recent increase of migrants/ Suboptimal coverage of screening and contact-tracing (high screening numbers, separate registers) Organizations /Public Health services understaffed regarding the workload (delay and difficulties in diagnosis, treatment, care and follow up/ Treatment &.care/ organise cross-border care /low compliance , many lost-to-follow-up under TB treatment and continuing migration mobility 22/36 (61.1%) Major barriers to access health care services related to cultural, religious, and language differences/ lack of knowledge about TB, lack of information about the healthcare system in the country and cultural constraints/Stigmatization of TB patients/ insufficient patient counselling and motivation 13/36 (36.1%) Lack of coordination among involved entities 6/36 (16.6%) Logistical problems 10/36 (27.7%)	Respirators used for staff and surgical masks for individuals with possible TB or other respiratory disease 24/36 (66.6%) Only Respirator used for staff in contact with refugees 1/36 (2.7%) Other 7/36 (19.4%) Not answered 4/36 (11.1%)

Footnotes: TB: tuberculosis

Discussion

The aim of our study was to investigate which reported policies and practices exist for TB and LTBI screening and management among refugees in low and intermediate TB incidence countries of Europe. The survey had a very high response rate (36 (94.7%) out of 38) which shows countries' interest and prioritisation of this issue.

The results of our study confirm that screening for TB is considered as an important public health measure in Europe, although significant differences exist in screening practices among countries.

According to a survey conducted in 2012 on screening practices on infectious diseases among newly arrived migrants to Europe, all countries perform TB screening, with the second-most screened condition being Hepatitis B (30% of the countries) [18]. The results of our survey also indicate that there is a general lack of analysis of the yield of TB and LTBI screening among refugees. The huge workload is assumed as the main reason. Furthermore, much less information is available for LTBI than for active TB disease.
While our survey shows that 31 countries regularly screen refugees for TB, only 19 screen for LTBI, and even a fewer report outcomes of LTBI treatment [9]. In view of TB elimination, more and more emphasis will be given to the possibility of implementing LTBI registers in low TB incidence countries [19].

Although 11 out of 36 countries answered they were equipped to collect information on LTBI screening, only three (Finland, Norway and the UK) confirmed collection of data, although not systematically. LTBI management remains a component of the TB Elimination strategy which is challenging countries, particularly when a large number of patients is involved. In fact, the large number of arrivals in holding centres, particularly in some European countries, makes LTBI screening and subsequent management problematic. In addition, several countries reported difficulties in coordination between holding centres and TB services serving the native population.

Based on our survey, it appears that there are no systematic follow-up screening/check-ups of refugees for TB sometime after their arrival. Given that refugees are often exposed to precarious, stressful travelling conditions during transit, which provide a risk of *Mycobacterium tuberculosis* transmission, there is a need to ensure people-centred care is available to them beyond arrival in their host country. Symptomatic screening of refugees and more intensive follow-up for those with LTBI may be justified. This is particularly important as many European countries are scaling-up their efforts to eliminate TB [10].

In an attempt to make screening as cost effective as possible, countries have applied different algorithms in-line with WHO recommendations [20]. According to our survey,

they are based on different combinations of symptom-baseds and chest radiography, with addition of bacteriology in a few countries (table 2). Evaluation of the yield of these screening procedures was beyond the scope of this study; however, there is a real need for analysis of such data at national and regional level [5, 6].

Our study identified different models of screening for TB/LTBI in Europe. Some countries perform radiological screening of all refugees in a hub or holding centre, and carry out further investigations in decentralised centres only if radiological abnormalities are identified. Others implement different screening algorithms or organise provision of health services differently at the refugee centres. In this context, screening for LTBI, by use of IGRAs and/or TST, although considered an important intervention in the pursuit of TB Elimination [9, 10] is still difficult to implement in several countries.

Based on the unprecedented number of refugees, it is important to have a specific response plan and ensure its full funding both at the national and European level. Interestingly, in the majority of countries (22 (61.1%) out of 36), TB services are organised in collaboration with NGOs and other sectors. Among others benefits, this approach has the advantage of increasing cultural sensitivity of the TB services.

Infection-control measures are generally inadequate in a large proportion of the countries surveyed. Surgical masks are often used to "protect" healthcare workers when it is well known that they are ineffective against *M. tuberculosis* from active TB patients who are not on treatment; certified respirators are needed for this purpose. Furthermore, a lack of specific training on infection control measures has been reported. Similar problems have previously been described in European MDR-TB reference centres [21].

Although surveys of this kind are subject to several limitations (related to the instrument used, the missing information from non-responding countries, the possible erroneous responses from national programmes and the limitations of aggregated data), strengths of this study include: continuous dialogue with National TB representatives; the very high response rate (94.7%); and the consistency of the answers received with previous surveys carried out using similar methodology [10].

The results of the present study highlight the need for improved coordination of TB screening in Europe, with the ultimate goal of implementing the End TB Strategy, the TB Action Plan for the WHO European Region 2016–2020 [22] and the Health 2020 Policy Framework [23] to address inequity. The ultimate goal of these strategies is to achieve TB Elimination [9, 10, 24, 25]. This will require quality operational research evaluating surveillance (aimed at attaining better data for better planning), the efficacy of existing algorithms and the yield of screening activities [26]. Furthermore, within the limited

information available on LTBI in the European context, further clinical and operational research is also needed to inform clinicians and public health authorities on the correct approach to follow when LTBI is diagnosed in contacts of MDR-TB cases.

Finally, the new function of the ERS/WHO Europe TB Consilium (a free, internet-based instrument supporting clinicians to manage difficult-to-treat cases of tuberculosis) is now live and accessible under the TB Consilium website (www.tbconsilium.org). This electronic platform will allow better cross-border TB control by contributing to the provision of quality prevention, diagnostic and treatment services to migrants and refugees.

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CHAPTER 10

General Discussion

This thesis covers several operational research studies on tuberculosis and drug resistance in the WHO European Region between 2010 and 2018. These studies can guide national health authorities and key stakeholders through evidence-informed decision making, focus on areas where there are still gaps in knowledge and utilise more effective interventions to end TB in the Region[1] to attain the sustainable development goals. The findings of the studies in this thesis and their impact on policies and practices are summarized in table 1.

Epidemiology of TB and extrapulmonary TB in the WHO European Region and evolution of international recommendations from DOTS to the Stop TB Strategy

The focus of most studies on tuberculosis is on the pulmonary forms of the disease, as these are the forms of the disease that are considered to be the primary source of infection at the community level. However, the extrapulmonary forms of the disease are equally important due to the suffering people go through, as well as their link with HIV coinfection, mortality and their more frequent occurrence in certain population groups. In **Chapter two**, we discussed that the WHO European Region Member States in general have a good level of data completeness, with only handful of countries not reporting the localisation of the disease. We also found out that the rate of reported multi-drug resistant TB is lower among extrapulmonary forms of the disease than among pulmonary TB (2.3% versus 5.2%). This may have to do with the fact that extrapulmonary TB is more common among migrants coming from countries with lower rates of drug resistant TB or the difficulties in obtaining adequate samples for culture growth, which at the time was the gold standard for identifying drug resistance. Examining these trends, we also found that the treatment outcomes for all patients showed decreasing trends from 2005 to 2010. As reflected in consecutive studies, including those in this thesis, we observed that this negative trend was halted, and that treatment outcomes began to increase slowly from 2010 onwards. As the international recommendations evolved from DOTS to the Stop TB strategy, we reviewed both strategies and argued that implementation of the wider Stop TB Strategy through people-centred integrated care, including all types of TB, calls for multidisciplinary approaches. Our study also identified gaps in surveillance and the need for more disaggregated data, including those on social determinants and HIV coinfection.

Cost effective plans to prevent and control drug resistant TB

Despite having less than 3% of all TB cases in the world, the WHO European Region has the highest rates of drug resistant tuberculosis and one in every five people with MDR-TB are from this Region, the majority being in eastern Europe and central Asia. In order to address this situation, a Regional Action Plan to Prevent and Combat M/XDR-TB was developed. In

[1] 'The 'End Tuberculosis Strategy' is aiming for a 95% reduction by 2035 in the number of TB deaths compared with 2015, a 90% reduction by 2035 in TB incidence rate compared with 2015, and zero TB-affected families facing catastrophic costs due to TB by 2035.

addition to early diagnosis and effective treatment of drug susceptible TB to prevent the acquisition of drug resistance, it is important to detect drug resistant TB in a timely fashion and provide adequate treatment to alleviate people's suffering and cut the transmission cycle. Globally, only about half of all patients with MDR-TB are successfully cured.[1] In order to assess the cost effectiveness of the proposed plan, using available data and resources, we developed a costing tool for the WHO European Region. In **Chapter three**, we used this costing tool and analysed the national and subnational data and found out that in high TB priority countries supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria, 78% of M/XDR-TB patients were successfully treated compared to 20% in other settings. This provided powerful evidence suggesting that the mobilisation of adequate funding from the Global Fund, other international donors as well domestic resources can make the difference in achieving the goals of the Action Plan. A transmission model, using epidemiological data reported to WHO, was then developed to calculate expected achievements. The WHO-CHOICE database[2] was used for the cost analysis. We calculated the cost of implementing the Action Plan at US$ 5.2 million for a period of five years. Implementation of the Plan, and in particular enhancing early TB detection and increasing treatment success while breaking the transmission cycle, would result in 263,000 M/XDR-TB cases averted, with a short-term economic gain of US$ 6.9 million. The long term economic indirect gain has not been determined but will be far greater than that in the short-term because many future transmission events were not considered in our study. Based on our analysis, investing in the prevention, early diagnosis and effective treatment of multidrug resistant TB is highly cost effective. The plan is expected to prevent the emergence of 250,000 new MDR-TB and 13,000 XDR-TB patients, respectively, saving US$7 billion and 120,000 lives. At the time of the study, we found out that there was a considerable projected funding gap of over 60% in order to fully implement the Plan. This study highlighted the urgent need for countries and international partners to increase funding for TB and MDR-TB prevention, diagnosis and treatment to have the desired impact. Furthermore, there is an identified need to invest in health systems that place an emphasis on patient-centred models of care. This is in line with the Action Plan and the European Health 2020 policy framework. Since the target of 75% treatment success of MDR-TB was not achieved, the final achievements may be less than those foreseen and deserve further analysis. It is noteworthy that, at the time of publication, new medicines have not yet been approved and shorter treatment regimens for drug resistant TB are not recommended.[3] This notwithstanding, the analysis provided useful information on the potential gains that supports the pillar of integrating patient-centred TB care and prevention within the TB action plan of the WHO Region and more broadly the need for more innovation and adapted models of care that can be guided by operational research. These findings support the need to increase the political commitment, provide further evidence for the investment case and underline the importance of increasing resources

and their efficient use in line with pillar two of the End TB strategy, as depicted in the conceptual framework of this thesis.

Using data at the national and subnational level to improve treatment outcomes and break the transmission cycle

Inadequate treatment of TB leads to unfavourable outcomes (death, treatment failure and loss to follow-up) and further transmission of disease. Unfavourable outcomes also negate the credibility of the TB programme in the eyes of health workers, patients and the community at large. In **Chapter four**, we analysed the reasons for unfavourable outcomes of more than 110,000 patients enrolled in treatment over a five-year period (2006-2010) in Uzbekistan, a high TB priority county. This is the largest study ever conducted in the Region. Our study showed that, 83% of patients were successfully treated, 6% died, 6% were lost to follow-up, 3% failed treatment and 2% were transferred out. Factors associated with death included being above 55 years of age, being HIV-positive, having a positive sputum smear result, having been previously treated, being jobless and living in certain provinces. Factors associated with loss to follow-up were being male, previously treated, jobless, living in an urban area and a resident of certain provinces. These findings highlight the need to have gender-specific and people-centred approaches to be able to reduce losses to follow-up. Having sputum smear positive pulmonary tuberculosis, being an adolescent, living in an urban population, being HIV-negative, previously treated, jobless and residing in particular provinces were associated with treatment failure. The considerable overlap of factors associated with the three specific adverse outcomes (death, treatment failure and loss to follow-up) suggests that similar social stratifiers are involved. These will need further in-depth research, but meanwhile being vigilant in following up and supporting individuals at risk would seem logical. Trends in unfavourable TB outcomes remained relatively stable over the five-year period, indicating that no additional measure is yet to play a significant role in reducing these proportions further. Some districts in the country revealed higher rates of unfavourable outcomes, particularly loss to follow-up. These findings calls for national programmes to continuously analyse both national as well as the subnational data, explore the reasons for unfavourable outcomes and address programmatic shortcomings, such as an overemphasis on centralised (hospital-based) models of care, insufficient staff and lack of psychosocial support. Our study also highlights the importance of analysing subnational data to identify actions that need to be taken at the national and district levels to adopt and implement people-centred policies and interventions that facilitate treatment adherence for patients and their families. These actions include expanding ambulatory services and mobile or home-based treatment, intensive management of adverse events, psychosocial support for patients and early detection of drug resistance and adaptation of treatment regimens accordingly. These efforts should lead to improved outcomes, alleviate suffering and break the transmission cycle. Moreover, our study shows that intersectoral collaboration and multidisciplinary

approaches are needed to address some of the determinants of unfavourable outcomes (e.g. imprisonment, unemployment and migration). The relatively high proportions of patients who were transferred out need to be addressed with improved recording and reporting measures and by implementing a case-based national register using digital health and real-time data management through which treatment outcomes are communicated, even if the patient is moved to another facility. Therefore, the importance of establishing and maintaining a robust online surveillance system across the country is a specific need that has been identified and could be bridged to fill gaps in surveillance and monitoring.

In **Chapter five**, we analysed the situation of drug resistant TB in 11 countries of eastern Europe and central Asia and proposed a way forward. TB incidence has been decreasing at about 5% per year and consequently the number of drug resistant TB cases has been decreasing; however, the MDR-TB rates have been stable in the majority of those countries, increasing in two countries and decreasing in five countries (Armenia, Estonia, Georgia, Latvia and Lithuania). Since first-line DST coverage has been below 80% in Azerbaijan, Bulgaria, the Republic of Moldova and Ukraine, we could not conclude that the decrease in MDR-TB proportion was a true decrease. At the time of publication, none of the 11 eastern Europe and central Asian countries had achieved the 75% regional target of successful treatment of MDR-TB. Three countries (the Republic of Moldova with 18 per 100,000 and the Russian Federation and Ukraine with 13 per 100,000 had the highest TB mortality rates), while this rate in EU/EEA countries stands below 1 per 100,000. We also concluded that over half of all TB deaths occurred in the Russian Federation. On a positive note, with various national and international initiatives including those facilitated by WHO, such as technical guidance and capacity building through the Green Light Committee,[3] treatment coverage of MDR-TB patients increased from 63% of estimated MDR-TB patients to 96% in 2013. Based on these data and country reports, we presented the main challenges as follows: a high level of resistance to fluoroquinolone and/or second line injectables as reported from various drug resistance surveys, very poor treatment success for drug resistant TB (as low as 28% in some settings) and unnecessary deaths and acquisition and/or transmission of drug resistance. Inadequate ambulatory and people-centred models of care like home-based care and over-emphasis on hospitalisation have contributed to nosocomial transmission and inadequate follow-up of patients outside hospital settings. At the time of publication, new rapid molecular diagnostic tests were not yet available in several countries and/or were not widely available to facilitate early TB detection. Furthermore, only three countries had achieved nationwide universal coverage of second line DST. The needs of vulnerable populations such as migrants, children, people living with HIV and prisoners are yet to be fully addressed. We concluded that there is a need for full commitment, funding and implementation of the Regional Action Plan. Furthermore, new medicines including bedaquiline, linezolid and delamanid have not yet

been approved for use in M/XDR-TB patients.[4] These measures, along with the possibility of full oral treatment regimens based on resistance patterns, need to be implemented fully across the Region to increase treatment success. We also highlighted that the spread of M/XDR-TB is driven by a complex interplay of factors, including inadequate treatment in terms of adherence and pharmacokinetics, a change in bacterial sensitivity towards resistance, as well as social and clinical determinants such as HIV, imprisonment, migration and socioeconomic factors. The concern is that, without further action, drug resistant strains of TB could become the dominant cause of TB in Europe.[5] Referring to the successful example of New York in the early 1990s, and successful countries like Latvia and Estonia, there is a need to address vulnerable and key populations who lie outside the realms of the routine health care system.

We concluded this chapter by discussing the need for integrating patient-centred TB care, bolder policies and support systems, as well as relevant operational research – these support all three pillars of the Tuberculosis Action Plan for the WHO European Region and provide equity in terms of 'leaving no one behind'.

The role of BCG in the WHO European Region

In **Chapter six**, we reviewed the role of BCG vaccination. BCG is currently the only available vaccine to protect against severe forms of TB, including meningitis in children. With the decline of TB incidence, several countries in Europe discontinued BCG vaccination at the national level.[6] With challenges in BCG procurement and supply, and after the interruption of production by Statens Serum Institute and changes to the BCG strain being administered, several countries observed increases in adverse events that were brought to media attention, risking breaching the population trust in immunisation. This prompted us to review the role of BCG by summarising current policies on vaccine administration and the management of adverse events of the BCG vaccine in the WHO European Region. Since its introduction in 1921, the BCG vaccine has been widely administered in the WHO European Region. However, with the decrease in the incidence of TB, many countries have moved to or are moving towards selective vaccination. In a few countries where the vaccination was suddenly stopped, an increase in severe forms of TB was noticed among children. We provided an overview of vaccination and revaccination policies in WHO European Region countries, which showed that policies at the country level varied widely. Most of the eastern European countries provide vaccination at birth, while many low incidence countries provide only selective vaccination.[7] All 18 high priority countries of the WHO European Region administer BCG at birth, from day 0 in Georgia up to 2 months of age in Turkey. Six of those countries revaccinated children before the age of 14 years old. Among the non-high priority countries of the Region, Albania, Croatia, Greenland (of Denmark), Hungary, Ireland, Monaco, Montenegro, Poland, Portugal, Serbia and Slovenia continue with BCG vaccination at birth. The risk of stopping BCG vaccination in a low incidence

country will need to be carefully balanced against the risk of an increase in TB amongst children. There is no evidence of a threshold incidence; however, the International Union Against Tuberculosis and Lung Disease (IUATLD) expert opinion suggests a threshold of less than 5 in 100,000 new sputum smear positive pulmonary cases before stopping herd BCG vaccination.[8] It is noteworthy that, even in low TB incidence countries, there may be a subset of the population, such as people who use injectable drugs, the Roma population and migrant populations, who have a higher risk of TB, and BCG vaccination should be made available to those groups. We also provided an overview of adverse events and using the existing data, and highlighted that there are currently no recommendations for the use of certain strains. This chapter provided evidence indicating the need for bolder policies and relevant operational research to use the BCG vaccine in settings with the highest expected impact, but also reiterate the underlying need for a new and more effective vaccine for TB.

TB in prisons and congregate settings

Prisons and congregate settings can be breeding grounds ('hotspots') for TB, particularly in eastern Europe and central Asia[9], and yet they can create an important opportunity for intensified case finding and timely and effective treatment, which will contribute to ending TB. In **Chapter seven**, we conducted a review of published articles on TB in penitentiary services between 1990 and 2014. In addition, we reviewed the conference abstracts from the International Union Against Tuberculosis and Lung Disease and WHO publications during the same period. We analysed the programmatic challenges and gaps in the evidence on TB in prisons that need to be addressed through research. Among 637 citations and 332 abstracts screened, 96 publications were used in our review. 21% of studies highlighted the lack of well-organised health systems and inadequate follow-up of released prisoners. Although new molecular diagnostic tests often do not require complicated infrastructure, several recent studies referred to the unavailability of these new diagnostic tests. High sensitivity and specificity GeneXpert MTB/RIF and its rapid results make it an excellent tool for screening for TB and rifampicin resistance in congregate settings. Health policy makers and authorities need to provide adequate resources to ensure the use of GeneXpert in the prison or transport of samples to laboratories outside of prisons. In terms of treatment, four studies referred to the suboptimal quality of TB medicines, while 30% of studies mentioned that treatment is not observed (supervised therapy) in their settings. These may stem from prison services not having adequate staff or psychosocial or behavioural problems in prisons. Within most prison systems, follow-up of released prisoners is limited or does not occur at all. 26% of studies reported that TB control in prisons is hampered by the prohibition to attend local clinics or hospitals for security reasons, and 31% of studies struggled with effective TB control due to prisoners being lost to follow-up and high turnover rates. Our review underlined the importance of facilitating data exchange and implementing interventions to reduce loss

to follow-up. In terms of HIV response, only seven studies mentioned the challenge of addressing TB/HIV coinfection. These studies highlighted key shortcomings such as a lack of awareness, increased stigma, weak counselling services, inadequate coordination of TB and HIV services, insufficient human resources and poor surveillance. In total, 18 studies documented interventions for latent TB infection, with varying levels of treatment completion due to the high turnover rate or release of prisoners. One fourth of the studies highlighted the importance of high-level commitment to ensure adequate resources. This is particularly important in eastern Europe and central Asia where there are high rates of drug resistant TB. As part of building political commitment, it is essential to ensure that both legislation and national guidelines facilitate TB prevention and control in prisons. Given the differences in the transmission dynamics and characteristics of this population, an up-to-date guideline outlining research priorities needs to be developed for correctional institutions. All national TB strategic plans should include priority interventions for the prevention and control of TB, drug resistant TB and TB/HIV coinfection in prisons. Based on our review of the existing evidence and gaps, we outlined the research gaps and the areas in which further evidence is needed for introducing more effective and efficient TB prevention and control in prisons. Research conducted in prisons needs to have a specific approach in terms of obtaining ethical clearance.[10] Our research in this chapter is in line with implementing people-centred care that is adapted to the needs of vulnerable and key populations who are often left outside the realms of the routine health system. Being able to reach these populations would help make a dent in missed TB cases and TB mortality as a whole.

New roadmap for childhood tuberculosis

Children represent a vulnerable population regarding TB, and this age group has not been adequately prioritised. In **Chapter eight**, we reviewed the TB situation in children and relevant policies in 18 high TB priority countries. In 2011, an estimated 23,000 children had tuberculosis, of whom nearly 5,000 were estimated to have had multidrug-resistant or extensively drug-resistant disease; however, only 1,000 children with TB had been reported.[11] This reflects the difficulty in diagnosing TB among children and/or the fact that the estimates are not accurate. While all participating countries reported contact tracing of close household contacts, only eight countries had policies for contact tracing children with close non-household contacts. Four countries only treat children with bacteriologically confirmed MDR-TB, while it is evident that there are fundamental difficulties in obtaining bacteriological confirmation in young children. In terms of preventive therapy, several countries provide prophylactic TB treatment for all children irrespective of age or the tuberculin skin test result. Only eight countries provide prophylactic TB treatment for children with HIV. In this Chapter, we concluded that countries need to prioritise early detection, preventive treatment and full TB treatment and care of children. This evidence highlighted the gap in achieving all three pillars of the TB Action Plan in the European

Region. As research on drug resistant TB among children is rare, so too is evidence on the most effective management of drug resistant TB in children. The WHO Regional Office for Europe prepared an expert opinion paper to update readers on recent scientific evidence as well as region-specific clinical and public health recommendations on child and adolescent MDR-TB.[12]

Response to the migrant crisis and tuberculosis

Most EU/EEA countries have a low TB incidence (as defined by a notification rate below 10 per 100,000 population); TB predominantly affects vulnerable populations, mainly migrants. In 2015 and 2016, the EU experienced an unprecedented influx of refugees and migrants. More than one million people arrived in the European Union, most of them fleeing from war and terror in Syria and other countries.[13] Many of the migrants were from countries with a moderate to high incidence of tuberculosis. Although TB in pre-conflict Syria was reported to be as low as 20 per 100,000, with several years of conflict and consequent population movements, precarious living conditions and difficult travel along migrant routes, TB rates may be higher among these people. In order to document the policies and practices of TB diagnosis and care services for migrants, in collaboration with the European Respiratory Society, we designed and conducted a survey in 38 countries of the WHO European Region, including the EU/EEA and transit countries that migrants passed through. In **Chapter nine**, we reviewed and analysed the results of this survey. A total of 36 out of 38 countries provided responses, showing that various algorithms for active TB case finding exist, including different combinations of symptom-based questionnaires, bacteriology and chest radiography. LTBI screening was reported as being conducted with different combinations of tuberculin skin tests and interferon-gamma release assays. In more than half of these countries, TB and LTBI screening were performed in refugee centres. Three quarters of the countries reported that they are adapting services to refugee-specific needs. This is an important aspect, as refugees have various fears and face stigma as well as the cultural and language barriers that need to be overcome with the help of migrant communities. Two countries stated that they were not doing any screening, as in one country the duration of stay of migrants was too short and the other country mentioned a lack of funding as a reason for not performing TB screening. The survey revealed that, despite the high mobility of migrant populations, countries do not have coherent policies and practices and there is little or no coordination, in addition to a lack of data exchange across national borders. Furthermore, the results of our survey revealed that infection control measures are inadequate in several of these countries. We identified that only one third of countries have the possibility of collecting data for LTBI. The detection and treatment of LTBI are crucial to prevent further development of TB in these vulnerable populations. This is a gap that needs to be addressed to move faster towards TB elimination in the EU/EEA. Our survey also revealed that more efforts are needed to share good practice and ensure a continuum of care across national borders. In order to end TB,

efforts need to be scaled up in all countries in the region, irrespective of where they are classified in terms of TB burden (low, moderate or high). Several other studies have been conducted by national experts, including in the Netherlands, presenting their experience and the results of TB screening among migrants. The Dutch experience showed that active TB screening among Syrians led to very low TB yield.[14] However, among Eritrean/Ethiopian asylum seekers, the prevalence and incidence in the first year in the Netherlands was high. This suggests that many of them had been recently infected, either in their country of origin or during the journey. Other interventions are required, such as screening for latent infection, to prevent tuberculosis among high-risk asylum seekers and further reduce the incidence of this disease in the Netherlands.[15]

It is likewise important that countries systematically review their screening practices for active and latent TB based on the methods used and their yield. Furthermore, there is a need to adapt policies and practices to improve the cross-border exchange of data in line with the Minimum Package of Cross Border TB Control and Care.[16] Although TB is not readily transmissible and health systems of low incidence countries are strong enough to absorb the increase in TB among migrants, public health authorities and practitioners need to prioritise TB screening and the provision of quality and timely treatment.[17] This is particularly important as TB is a rare disease in low incidence countries and its symptoms may go unnoticed for a while. Finally, this survey also highlights the need to reach out and adapt health systems in an innovative manner to reach vulnerable populations. This cannot be achieved without bold policies and supportive systems that cross national borders.

Table 1. Summary of findings of operational research studies in this thesis and their impact on policy and practices

Chapter Name and Citation of the article	Key objective	Methodology	Key findings	Implications and impact on policy and practice
Chapter 2: Dara M, Dadu A, Kremer K, Zaleskis R, Kluge HH, Epidemiology of tuberculosis in WHO European Region and public health response Eur Spine J (2013) 22 (Suppl 4): S549–S555, DOI 10.1007/s00586-012-2339-3	To provide an overview of the tuberculosis (TB) and multi-drug resistant tuberculosis (MDR-TB) in the WHO European Region and evolution of public health response with focus on extra-pulmonary tuberculosis and Pott's disease.	The annual TB surveillance and monitoring data submitted to WHO in 2005 and 2010 were analyzed and the elements of the global strategies and regional action plan were examined	In the past five years, treatment success had been decreasing while drug resistant TB and TB/HIV coinfection are on the rise in the Region. Only less than 1% of TB cases are reported as unknown disease location. There is a higher rate of extrapulmonary TB in EU/EEA countries than in non-EU/EEA countries (22% versus 16%). Countries with higher proportion of TB among foreign born have higher rates of extrapulmonary forms of the disease. Only EU/EEA countries reported the drug resistance among extrapulmonary patients, and this rate was lower than that of pulmonary patients.	There is a need for more granular data such as drug resistance rate among extrapulmonary TB in non-EU/EEA countries. The surveillance system shall also cater disaggregating data for HIV coinfection, risk factors and social determinants. As countries are moving towards case-based surveillance data, these analyses will be made possible. Through adopting new strategies, countries need to adapt services to all patients including extrapulmonary disease. This study highlighted the need for new diagnostic tests which can identify drug resistance faster including among extrapulmonary patients. https://www.cochrane.org/CD012768/INFECTN_xpertr-mtbrif-test-diagnosing-extrapulmonary-tuberculosis-and-rifampicin-resistance The global and regional reports also included more data on extrapulmonary forms of the disease. https://www.ecdc.europa.eu/en/publications-data/tuberculosis-surveillance-and-monitoring-europe-2014 Finally this study raised the alarm on the decreasing trends of treatment outcomes. As a result, national and international efforts were scaled up and the region managed to halt this negative trend and improvements were seen in the treatment outcomes thereafter. This increase still does not reach the regional targets and hence rapid diagnosis, new treatment regimen and more people-centred integrated models of care are to be further scaled up.
Chapter 3: Jakab Z, Acosta CD., Kluge HH, Dara M, Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-resistant Tuberculosis in the WHO European Region 2011 – 2015: cost-effectiveness analysis, Tuberculosis (2015), http://dx.doi.org/10.1016/	To assess cost effectiveness of the five-year Action Plan to prevent and Combat M/XDR-TB, with the expected achievements of diagnosing 85% of estimated MDR-TB cases and treating at least 75% successfully.	A transmission model, using epidemiological data reported to WHO was developed to calculate expected achievements. WHO-CHOICE database was used for cost analysis.	This plan was found to be highly cost-effective and expected to prevent the emergence of 250 000 new MDR-TB and 13,000 XDR-TB patients respectively, saving US$7 billion and 120 000 lives.	WHO Member States endorsed the Plan at the 65th WHO Regional Committee, aligning their national action plans and implementing strategies as recommended in the plan. This helped move forward with improving early detection and full access to treatment of drug resistant TB. The treatment success rate for drug-resistant TB in the Region improved from 48% in 2016 (cohort of 2011) to 55% in 2018 (cohort of 2015). Several countries with a high MDR-TB burden have managed to achieve remarkable success in curing more than 70% of MDR-TB patients, such as Kazakhstan and Latvia. (http://www.euro.who.int/en/about-us/governance/regional-committee-for-europe/past-sessions/68th-session/documentation/working-documents/eurrc688A-progress-reports)

Chapter 4: Gadoev J, Asadov D, Tillashaykhov M, Tayler-Smith K, Isaakidis P, Dadu A, de Colombani P, Gudmund S, Parpieva N, Ulmasova D, Jalolov A, Atadjan Hamraev A, Ali E, van den Boom M, Hammerich A, Gozalov O, Dara M. (2015), Factors Associated with Unfavorable Treatment Outcomes in New and Previously Treated TB Patients in Uzbekistan: A Five Year Countrywide Study. PLoS ONE 10(6): e0128907. doi:10.1371/	To determine trends in unfavorable outcomes (lost-to-follow-ups, deaths and treatment failures) and describe their associations with socio-demographic and clinical factors in Uzbekistan.	A countrywide retrospective cohort study of all new and previously treated TB patients registered in the National Tuberculosis programme between January 2006 and December 2010.	Among 107,380 registered TB patients, 67% were adults, with smaller proportions of children (10%), adolescents (4%) and elderly patients (19%). Pulmonary TB was present in 77%, of which 43% were smear-positive and 53% were smear-negative. Overall, 83% of patients were successfully treated, 6% died, 6% were lost-to-follow-up, 3% failed treatment and 2% transferred out. Being previously treated, jobless and living in certain provinces were independently associated with all three adverse outcomes namely death, lost to follow up and failure. In addition, death was associated with being above 55 years of age, HIV-positive and sputum smear positive, while lost-to-follow-up was associated with being male. Having smear positive PTB, being an adolescent, and being HIV-negative, were associated with treatment failure.	This study provided the evidence to improve TB services for certain vulnerable groups and in specific areas of the country. Specifically, the study advocates for the development of unified monitoring and evaluation tools for drug-susceptible and drug-resistant TB and calls for better TB surveillance and coordination between provinces and neighboring countries. Between 2009 and 2018, the TB mortality rate at regional level fell cumulatively by 57%, from 5.8 to 2.5 deaths per 100 000 population, which on average is a decline of 9.1% per year. This decline was over 12% between 2017 and 2018, which is notably higher than the global rate of decline for TB mortality (3.6% between 2017 and 2018) (http://www.euro.who.int/en/about-us/governance/regional-committee-for-europe/past-sessions/68th-session/documentation/working-documents/eurrc688A-progress-reports)

Chapter 5: Acosta CD, Dadu A, Ramsay A, Dara M. Drug-resistant tuberculosis in Eastern Europe: challenges and ways forward. Public Health Action. 2014;4(Suppl 2):S3–S12. doi:10.5588/pha.14.0087	To review drug-resistant TB in the eastern European Europe; the challenges to MDR- and XDR-TB control; and potential ways forward.	Cross-sectional study involving primary data collection	While only approximately 4% of the global burden of TB was found in the WHO European Region, a total of 25% of the world's burden of MDR-TB is also found here, indicating the crucial importance of MDR-TB for this region. There is an increasing XDR-TB rate among drug-resistant cases. Among new and previously treated cases, MDR-TB treatment success rates have decreased from respectively 72.5% and 50% in 2005 to 66.1% and 46.5% in 2012. In total, only 49% of people diagnosed with MDR-TB had a successful treatment outcome, well below the 75% target. All countries in Eastern Europe have developed national MDR- and XDR-TB response plans in consultation with the WHO. Despite widespread coverage of second-line drugs, there is still inadequate treatment and insufficient patient support mechanisms in some Eastern European countries with overreliance to hospitalization, including some member states of the European Union.	A policy decision was taken to support the Member States adapt individualized treatment regimens based on drug resistance patterns. In order to increase treatment success, rapid molecular diagnostic techniques are to be scaled up rapidly. Countries were guided to administer the recently approved two new medicines (bedaquiline and delamanid). Health system challenges including inadequate human resources, over emphasis on hospitalization are to be addressed. WHO Regional Office and key partners led a three-year project to improve people centered care in 11 countries 2015-2018. According to 2016 base line data, the number of countries, which have adopted key policies on health system strengthening and TB was relatively low at around 45%. The repeat survey in 2018, showed that more than 73% of the countries introduced key policies on people-centred TB prevention and care in 2017, which shows an increase of almost 50% compared to the baseline. During the same period the average length of hospital stay was reduced from 73 to 30 days in the target countries. Winter R, Perehinets I, Dara M, van den Boom M, Bivol S and Kluge H. People-centred TB prevention and care in eastern Europe and central Asia Eurohealth — Vol.24 | No.4 | 2018

Chapter 6: Dara M, Acosta CD, Rusovich V, Zellweger JP, Centis R, Migliori GB, Bacille Calmette–Guérin vaccination: the current situation in Europe, European Respiratory Journal, Jan 2014, 43 (1) 24-35; DOI: 10.1183/09031936.00113413	To review the evidence and present an overview of BCG vaccination policies in WHO European Region	Policies and practices of BCG vaccination in WHO European Region and WHO and other International recommendations summarized	BCG is currently the only available vaccine against tuberculosis. Despite its limitations, it offers reasonable protection against severe forms of tuberculous disease among children. Among 18 high TB priority countries in WHO European Region, all administer BCG at birth from 0 day in Georgia up to 2 months in Turkey and six of those countries do revaccination up to 14 years old. Among the non-high priority countries of the Region Albania, Croatia, Greenland (of Denmark), Hungary, Ireland, Monaco, Montenegro, Poland, Portugal, Serbia, and Slovenia continue with BCG vaccination at birth	This review highlighted the need for low TB incidence countries to balance the risk of stopping BCG vaccination in against the risk of an increase in tuberculosis among children in the risk groups e.g. Roma or migrant population. The evidence from this study added to the advocacy for more effective vaccine for TB among general population

Chapter 7: Dara M, Acosta CD, Vinkeles Melchers NVS, Al-Darraji HAA, Reyes H, Centis R, Sotgiu G, D'Ambrosio L, Ghadha SS, Migliori GB: Tuberculosis control in prisons: current situation and research gaps; International Journal of Infectious Disease, March 2015 Volume 32, Pages 111–117	To describe research gaps in TB in prisons	Review of published articles and WHO publications on TB in penitentiary services between 1990 and 2014, and assess them through the End TB strategy to identify the research gaps	Among 637 citations and 332 abstracts screened, 96 publications were used in our review. 21% of studies referred to lack of well-organized health systems and inadequate follow-up of released prisoners. several recent studies referred to unavailability of these new diagnostic tests. In terms of treatment, four studies highlighted suboptimal quality of TB medicines, while 30% of studies mentioned treatment is not directly observed in their settings. Within most prison systems, follow-up of released prisoners is limited or does not occur at all. 26% of studies reported that TB control in prisons is hampered by the prohibition to attend local clinics or hospitals due to security reasons, and 31% of studies struggled with effective TB control due to prisoner's loss to follow up and high turnover.	Our study identified further areas where research is needed to address TB in prisons. In 2019, WHO Regional Office complied a compendium of good practices on TB prevention and control in prisons (http://www.euro.who.int/en/publications/abstracts/compendium-of-good-practices-in-the-implementation-of-the-tuberculosis-action-plan-for-the-who-european-region-20162020 , accessed 30 October 2019). High sensitivity and specificity of GeneXpert MTB/RIF and its ability to provide rapid results make it an excellent tool for screening for TB and Rifampicin resistant in congregate settings. Health policy makers and authorities need to provide adequate resources to ensure use of GeneXpert in the prison or transport of samples to laboratories out of prisons. Closer collaboration and/or coordination of prison and civilian health services is needed to ensure continuum of care
Chapter 8: Acosta CD, Rusovich V, Harries AD, Ahmedov S, van den Boom M, Dara M, A new roadmap for childhood tuberculosis, The Lancet Global Health, Volume 2, Issue 1, PE15-E17, January 01, 2014, DOI: https://doi.org/10.1016/S2214-109X(13)70153-0	To review TB situation in children and relevant policies in the 18 high TB priority countries of WHO European Region	Design, collection and analysis of a survey on national policies and practices to address TB in children	From 23 000 estimated TB and 5000 estimated MDR-TB cases among children, only 1000 children were notified in 2011, only eight countries have policies for contact tracing for children with close non-household contacts. Four countries treat only children with bacteriological confirmed MDR-TB. Only eight countries providing prophylactic treatment for children with HIV	Result of survey showed TB in children is largely a neglected area. This study led to countries in the region being asked to update and fully implement national policies for TB prevention and control among children. In 2018 WHO Regional Office for Europe worked with a group of international experts and issued an Expert Opinion: Multidrug-resistant tuberculosis in children and adolescents in the WHO European Region, Expert opinion. Copenhagen: WHO Regional Office for Europe; 2019. Licence: CC BY-NC-SA 3.0 IGO. https://apps.who.int/iris/bitstream/handle/10665/329395/9789289054447-eng.pdf

Chapter 9: Dara M, Solovic I, Sotgiu G, D'Ambrosio L, Centis R, Tran R, Goletti D, Duarte R, Aliberti S, de Benedictis FM, Bothamley G, Schaberg T, Abubakar I, Teixeira V, Ward B, Gratziou C, Migliori GB, Tuberculosis care among refugees arriving in Europe: a ERS/WHO Europe Region survey of current practices European Respirtory Journal 2016 Sep;48(3):808-17. doi: 10.1183/13993003.00840-2016. Epub 2016 Aug 4.	To document policies and practices on TB screening and management among refugees and migrant population in low to middle incidence countries of WHO European Region	Design, collection and analysis of a survey on national policies and practices to detect and treat latent and active TB among refugees, asylum seekers and migrant population	Out of the 36 responding countries, 31 (86.1%) reported screening only for active TB and 19 for Latent and active TB infection. Screening for TB is based on various algorithms including different combinations of symptom-based questionnaires, bacteriology and chest radiography. LTBI screening was reported as being conducted by different combinations of tuberculin skin test and interferon-gamma release assays. In 22 (61.1%) countries, TB and LTBI screening are performed in refugee centres. Two countries mentioned they are not doing any screening as in one country duration of stay of migrants are too short and the other country mentioned lack of funding, as the reason. Half of the countries (8/17) which were not performing screening for TB and LTBI, plan to introduce it for TB and/ or LTBI in the near further. In more than half of countries responding, there is a legal framework for screening. In 22 (61.1%) countries, TB services are organized in collaboration with the private sector.	Despite the growing migrant issue affecting Europe, countries do not have coherent policies and practices and there is little, if any coordination and exchange of data across national borders. Detection and treatment of LTBI are crucial to prevent further development of TB among vulnerable populations Furthermore, infection control measures are inadequate in several of the countries. This calls for a more coordinated approach and the need to establish a common data base. The WHO Regional Office for Europe in collaboration with countries are trying to address these gaps with the Members states. The WHO Regional Office, through the Health Evidence Network, conducted a literature review of the available evidence for screening and management of TB among migrants and refugees. http://www.euro.who.int/en/health-topics/communicable-diseases/tuberculosis/publications/2018/what-constitutes-an-effective-and-efficient-package-of-services-for-the-prevention,-diagnosis,-treatment-and-care-of-tuberculosis-among-refugees-and-migrants-in-the-who-european-region-themed-issues-on-migration-and-health,-viii-2018

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Samenvatting

Samenvatting (summary of this thesis in Dutch)

Hoewel tuberculose (TBC) een oude ziekte is, zorgt het nog steeds voor een significante last op de mensheid. Naar schatting is één vierde van de wereldbevolking ermee geïnfecteerd. Jaarlijks ontwikkelen ongeveer 10 miljoen mensen de actieve ziekte en zijn er ongeveer 1,5 miljoen sterfgevallen. In de Wereld Gezondheid Organisatie (WGO) Europese Regio wonen ongeveer 900 miljoen mensen, verspreid over 53 landen, welke erg divers zijn op het gebied van sociaaleconomische ontwikkeling en zorgsystemen. Deze diversiteit is ook terug te zien in de grote verschillen in TBC-incidentie en sterftecijfers tussen de landen van de Regio. Ondanks dat slechts 3% van de globale casussen in de Europese Regio voorkomt, huist het één vierde van alle patiënten met *Multi-drug resistant* TBC (MDR-TB) ter wereld. Sinds 2010 heeft de WGO, met bijdrage van haar lidstaten en partners, twee 5-jaar Actieplannen ontwikkeld om TBC en MDR-TB aan te pakken. Met behulp van de Wereldgezondheidsvergadering *(World Health Assembly)* en de resoluties van de WGO Regionale Commissie (*WHO Regional Committee*) voor Europa, hebben de overheden samen met donors en gemeenschappen zich toegewijd aan het elimineren van TBC. Ondanks de snelste daling in incidentie (ongeveer 5% per jaar) van TBC ooit, zijn de behandelingen nog niet succesvol genoeg. TBC blijft kwetsbare groepen disproportioneel aantasten. Het doel van de onderzoeken van dit proefschrift is bewijs te genereren voor het verbeteren van het TBC-beleid en behandeling in de WGO Europese Regio. De onderzoeken zijn opgebouwd op basis van de drie pijlers van de *'WHO End TB Strategy'* (Geïntegreerde Patiëntenzorg, Sterk Beleid en Onderzoek en Innovatie). De doelstellingen van dit proefschrift zijn: 1) Het evalueren van de epidemiologie van TBC in de WHO Europese Regio, de volksgezondheidsmaatregelen en de kosteneffectiviteit van MDR-TB preventie- en controleplan: Dit wordt beschreven in hoofdstuk twee en drie. 2) Evalueren hoe de uitkomsten van TBC-behandelingen verbeterd kunnen worden in verschillende TBC categorieën: Dit wordt beschreven in hoofdstuk vier en vijf. In hoofdstuk vier kijken we naar nationale en sub-nationale data van een land met een hoge TBC-incidentie en schetsen we een beeld van de ongunstige uitkomsten, welke kunnen leiden tot onnodige sterfte, ongeremde transmissie en de opkomst van medicatieresistentie. In hoofdstuk vijf analyseren we de situatie in Oost-Europa en Centraal-Azië. 3) Het evalueren van de rol van BCG-immunisatie in de preventie van TBC: In hoofdstuk zes bespreken we de gegevens van momenteel beschikbare vaccins bij kinderen en praktijken in de regio. 4) Het analyseren van de bestrijding van TBC in kwetsbare bevolkingsgroepen. In hoofdstuk zeven, acht en negen analyseren we deze aspecten met betrekking tot TBC-preventie en zorg in een gevangenissetting, in kinderen en in migranten.In onze operationele onderzoeken hebben we zowel jaarlijkse surveillancegegevens, die gerapporteerd zijn aan de WGO en de ECDC tussen 2005 en 2018 gebruikt, als specifieke nationale ziekteregistratie en enquêtes van 2010 tot 2018. We bespreken onze bevindingen middels een grondige analyse van de data en bieden een toekomstbeeld.

Doelstelling 1

In **hoofdstuk twee** evalueerden we de epidemiologie van tuberculose in de WHO Europese Regio en de evolutie van de volksgezondheidsmaatregelen van 2005 tot 2010. We hebben ook vastgesteld dat, ondanks de grote variaties in het aandeel extra-pulmonale TB onder alle TB-patiënten in alle landen (varieert van 4% tot 47%), het aandeel over de laatste vier jaar relatief stabiel is gebleven (17%). Onze studie stelde ook vast dat de werkzaamheid van de behandeling voor pulmonale tuberculose daalt (72,5% tot 68,7% voor nieuwe patiënten en 50% tot 47,6% voor herbehandelingen), terwijl het aandeel van MDR-TB onder alle TBC-patiënten stijgt van 4,3% naar 7,5%. We bespraken dat de Regio zich moet aanpassen en de uitgebreide 'Stop TB Strategy' moet implementeren om deze problemen te bestrijden.

In **hoofdstuk drie** presenteerden we met gebruik van een transmissiemodel de verwachte resultaten van het 'Consolidated Action Plan to Prevent and Control Multidrug- and Extensively Drug-resistant Tuberculosis in the WHO Region 2011-2015'. Daarnaast creëerden we een model, waarin we de kosten van de opsporing en behandeling van M/XDR-TB-patiënten en de besparing die het zou opleveren berekenden. We concludeerden dat de implementatie van het Actieplan zeer kosteneffectief is. Verwacht wordt dat het 250.000 nieuwe MDR-TB en 13.000 XDR-TB casussen kan helpen voorkomen. Dit bespaart 7 miljard Amerikaanse dollars en redt 120.000 levens.

In **hoofdstuk vier** evalueerden we de nationale en sub-nationale data van meer dan 107.000 nieuwe en opnieuw behandelde TBC-patiënten van 2006 tot 2010 in Oezbekistan. Hierbij keken we naar de relevante demografische factoren en de varianten die van invloed zijn op de behandelingsuitkomsten. Factoren geassocieerd met verlies van follow-up zijn: Het mannelijk geslacht, eerdere behandeling, werkeloosheid, wonen in een stedelijk gebied en wonen in bepaalde provincies. Factoren geassocieerd met het falen van de behandeling, zijn: Het hebben van een sputumkweek-positieve pulmonaire TB, jongvolwassenheid, wonen in een stedelijk gebied, HIV-negatieve status, eerdere behandeling, werkeloos en wonen in bepaalde provincies. Hoewel de nationale data van 83% succesvolle behandeling als een grote prestatie kan gezien worden, hebben de analyses van sub-nationale data een licht geworpen op de hoogste risicofactoren voor ongewenste uitkomsten. Deze analyses kunnen een richtlijn bieden voor nationale programma's en lokale autoriteiten in de strijd tegen TBC.

In **hoofdstuk vijf** analyseerden we de trends en de proporties van MDR-TB onder alle TBC-casussen in 11 landen in Oost-Europa en Centraal-Azië. We evalueerden de 'First-line drug susceptibility testing' (DST), succespercentage van behandeling, evenals de data van TB onder kwetsbare groepen (gedetineerden, mensen met HIV, kinderen en migranten). We stelden ook vast dat data over tweedelijnsmedicatie niet altijd verzameld

wordt en dat het succespercentage van behandeling bij XDR-TB slechts 28% is. We keken naar de uitdagingen, met name het budgettaire deficit van 60% in 2011, welke de succesvolle preventie en controle van medicatie-resistente TBC in de weg staan en bieden een toekomstperspectief. We beschreven de noodzaak toegang tot snelle moleculaire diagnostiek te vergroten en om nieuwe medicatie zoals bedaquiline te introduceren en beschikbaar te maken. Ook moet er gewerkt worden aan het verkorten van de behandelduur, en het vergroten van de bewegingsvrijheid van patiënten met TB behandeling.

Doelstelling 2

In **hoofdstuk zes** presenteerden we, na het verstrekken van een overzicht van de geschiedenis, veiligheid en productie van BCG, de beschikbare beleidsopties en aanbevelingen. We presenteerden een overzicht van beleid van BCG-vaccinatie in de landen van de WGO Europese Regio in 2013. In alle 18 landen waar TBC een hoge prioriteit heeft, wordt BCG na de geboorte toegediend. Enkelen dezer landen dienen het vaccin een tweede maal toe aan 7 of 14-jarigen. In landen waar TBC minder prioriteit heeft (met name West-Europese landen met een lage TBC-incidentie) is BCG geen deel van het Nationaal Immunisatie Programma, hoewel het in sommige landen aan bepaalde groepen wordt gegeven. Naar mate meer landen in de lage TBC-incidentiecategorie vallen (minder dan vijf nieuwe casussen met sputumkweek-positieve per 100.000 inwoners per jaar), kan er vaker gekozen worden om BCG niet meer standaard toe te dienen. Landen kunnen er wel voor kiezen om BCG-vaccinaties beschikbaar te stellen aan kinderen die in hoog-risico gezinnen worden geboren.

Doelstelling 3

In **hoofdstuk zeven, acht en negen** evalueerden we de data en het beleid voor de bestrijding van TBC in kwetsbare groepen (gedetineerden, kinderen en migranten). Hoofdstuk zeven behandelt de data van gedetineerden in de Europese Regio. Gevangenschap verhoogt het risico op TBC aanzienlijk (22 keer hoger in gevangenissen dan in de rest van de bevolking). Het gemiddelde meldingspercentage in gevangenissen in de Regio was 749 per 100.000 inwoners in 2018. We presenteerden de obstakels voor TBC-preventie en zorg in gevangenissen in lijn met de 'Stop TB Strategy', en bespreken de gebreken in het beschikbare onderzoek en bewijs. Bekende uitdagingen zijn onder andere ontoereikende laboratoriumcapaciteit, diagnostische middelen en voorraad van medicatie, slechte integratie tussen het TBC-beleid in gevangenissen en daarbuiten, inadequate infectiepreventie en lage prioriteit voor gezondheidszorg in gevangenissen.

In **hoofdstuk acht** presenteerden we de resultaten van een onderzoek naar de implementatie van door de WGO aanbevolen richtlijnen voor preventie, detectie en behandeling van TBC en medicatie-resistente TBC onder kinderen in 18 hoge-prioriteit-

landen. Ons onderzoek laat zien dat veel landen in Oost-Europa en Centraal Azië deze richtlijnen, welke in lijn zijn met de *'roadmap for childhood TB: towards zero deaths'*, niet volledig implementeren. In 2011werden er naar schatting 23.000 kinderen met tuberculose getroffen, waarvan bijna 5.000 met MDR-TB of XDR-TB. Deze schattingen staan in sterk contrast met de gerapporteerde cijfers van minder dan 1.000 kinderen met TBC in deze landen.

In **hoofdstuk negen** herzien we TBC screening- en behandelingsbeleid bij vluchtelingen. In 2015 bereikten meer dan één miljoen migranten en vluchtelingen Europa over land of zee, veel hiervan kwamen uit een land met een hoge incidentie van TBC. In 2014 was dit getal naar schatting lager (219.000). Er was geen recente data bekend over het beleid voor actieve en latente TBC-screening en behandeling onder vluchtelingen. Om hier informatie over te verkrijgen, stuurden we een enquête naar vertegenwoordigers van 38 nationale TBC-programma's van landen met laag of laag-gemiddelde TBC-incidentie in de Europese Regio. Van de 36 respondenten, screenen 31 voor actieve TBC en 19 voor Latente TBC Infectie (LTBI) waarvan slechts acht de resultaten van LTBI-behandelingen rapporteerden. Infectiepreventie was niet adequaat in meerdere landen die onderzocht werden. Internationale TBC-preventie en zorg voor migranten en vluchtelingen is uiterst belangrijk. We toonden aan dat er significante verschillen zijn in het TBC-screening-en behandelbeleid, en de implementatie ervan. . Verbeterde coördinatie van TBC-screening en -behandeling in Europa is nodig om de *'End TB Strategy'* succesvol te toe te passen en de ziekte uiteindelijk te elimineren.

Hoofdstuk tien biedt een overzicht gebaseerd op de bevindingen van de onderzoeken in dit proefschrift en de implicaties en invloed op het beleid.

A

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Other publications of the author

Other publications of the author

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